(12) UK Patent Application (19) GB (11) 2 124 614 A

(21) Application No 8314782
(22) Date of filing 27 May 1983
(30) Priority data
(31) 8219052
(32) 1 Jul 1982
(33) United Kingdom (GB)
(43) Application published
22 Feb 1984
(51) INT CL³
C07D 499/00 A61K 31/43
31/545/ C07D 501/00//
C07C 43/205 69/00
79/00 103/127 C07D
205/08 257/04 403/12
(52) Domestic classification
C2C 1310 1313 1314
1464 200 214 215 220
227 22Y 231 242 247 248
250 251 252 256 259 25Y
26X 275 281 28X 292
298 29Y 304 305 30Y 313
31Y 321 32Y 332 338 339
33Y 342 34Y 350 351 352
358 360 362 364 366 367
368 36Y 373 37Y 390 409
40Y 440 462 463 464 465
46X 491 49X 500 509
50Y 519 552 591 614 621
624 628 62X 633 634
638 652 658 65X 660
661 662 678 681 699 774
AA AB BZ KE KP MK QS RV
TB WP WS
C3S 120 122 139 141
142 143 152 163 169 171
173 210 212 220 222 223
361 440 QL
U1S 1347 2410 C2C C3S
(56) Documents cited
None
(58) Field of search
C2C

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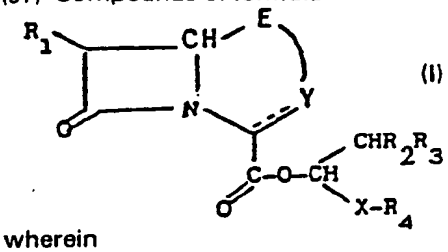
(54) Easily cleavable carboxylic esters and their use in the synthesis of penems and other β-lactam antibiotics

(57) Compounds of formula



(I)

wherein

R_1 is hydrogen, halogen or an organic group;

R_2 and R_3, being the same or different, are hydrogen or an organic group;

R_4 is an aromatic or hetero-aromatic, monocyclic or bicyclic ring, unsubstituted or substituted by one or more substituents chosen from: C_1—C_6 alkyl, C_1—C_6 alkoxy, formyl phenyl, phenoxy, C_2—C_6 alkanoyl, benzoyl, C_{1-6} alkoxycarbonyl, amino optionally substituted by one or two C_1—C_6 alkyl, formylamino, C_2—C_6 acylamino, benzoyl-amino, halogen and nitro;

the symbol —E— represents —O—; —S— or —CH_2—;

X is oxygen or sulphur; and

the symbol ---Y) represents a group completing, with the group —E— and the fused azetidinone ring, the skeleton of a β-lactam antibiotic; and the salts thereof.

These esters can be readily hydrolysed to the corresponding fre acids which have a broad spectrum *anti-bacterial activity.*

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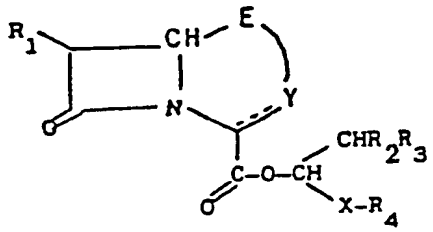
SPECIFICATION

Easily cleavable carboxylic esters and their use in the synthesis of pen ms and other β-lactam antibi tics

The present invention relates to new carboxylic esters of β-lactam antibiotics, to a process for their preparation and to certain useful intermediates of the said process.

The compounds of this invention have the general formula (I)



(I)

wherein

R_1 is hydrogen, halogen or an organic group;

R_2 and R_3, being the same or different, are hydrogen or an organic group;

R_4 is an aromatic or heteroaromatic, monocyclic or bicyclic ring, unsubstituted or substituted by one or more substituents chosen from: C_1—C_6 alkyl, C_1—C_6 alkoxy, formyl, phenyl, phenoxy, C_2—C_6 alkanoyl, benzoyl, C_1—C_6 alkoxycarbonyl, amino unsubstituted or substituted by one or two C_1—C_6 alkyl, formylamino, C_2—C_6 acylamino, benzoylamino, halogen and nitro;

the symbol —E— represents —O—; —S— or —CH_2—;

X is oxygen or sulphur; and

the symbol  represents a group completing, with the group —E— and the fused azetidinone ring, the skeleton of a β-lactam antibiotic. The scope of the invention includes also the salts and all the possible isomers of the compounds of formula (I), e.g. geometrical and optical isomers, and the mixtures thereof.

The alkyl, alkoxy, alkanoyl, alkoxycarbonyl, alkylamino and acylamino groups may be branched or straight chain groups. A halogen atom is for example chlorine, bromine or fluorine. An aromatic or heteroaromatic, monocyclic or bicyclic ring when substituted is preferably substituted by 1 to 3 substituents.

When R_1 is halogen, it is preferably chlorine, bromine or iodine.

When R_1 is an organic group, it is, for example, an acylamino group, a free or protected amino group or a substituted or unsubstituted aliphatic hydrocarbon groups. In particular, when R_1 is an acylamino group, it is preferably a substituted C_2—C_8 alkanoylamino group, in particular a substituted acetylamino group, still preferably a) an arylacetamido group, in which the term aryl stands for an aromatic homocyclic or heterocyclic radical, unsubstituted or substituted by one or more substituents chosen from C_1—C_{12} alkyl, halogen, hydroxy and amino; or b) a phenoxyacetamido group; or c) a 2-aryl-2-methoxyiminoacetmido group, wherein the term aryl stands, preferably, for phenyl, 2-furyl, 2-thienyl or 2-aminothiazol-4-yl.

When R_1 is a protected amino group, it is, for example, a straight or branched C_1—C_6 alkoxycarbonylamino group, e.g., tert-butoxycarbonylamino; or it is an imine, preferably a Schiff base with an aromatic aldehyde; or it is a C_2—C_6 substituted or unsubstituted acylamino, or a formylamino group; still preferably it is formylamino, acetamido and chloroacetamido.

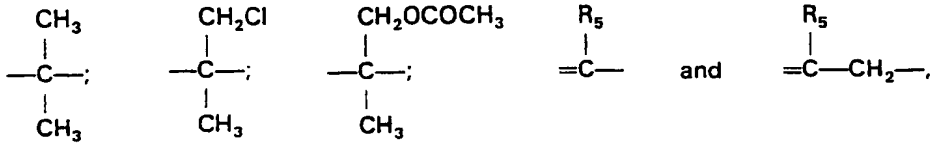
When R_1 is a substituted or unsubstituted aliphatic hydrocarbon group, it is, e.g., a radical chosen from C_1—C_{12} alkyl and C_4—C_7 cycloalkyl, wherein said radical is unsubstituted or substituted by one or more substituents chosen from hydroxy, amino, cyano and mercapto and in which the hydroxy, amino and mercapto groups can be free or in a protected form; preferred protecting groups for amino, hydroxy and mercapto groups are those known from the chemistry of peptides and β-lactam antibiotics. When R_1 is a substituted or unsubstituted aliphatic hydrocarbon group, it is preferably ethyl or 1-hydroxyethyl.

When R_2 and/or R_3 is an organic group, it is for example C_1—C_6 alkyl, preferably C_1—C_3 alkyl. R_2 and R_3, being the same or different, are preferably hydrogen or methyl.

When R_4 is an aromatic monocyclic ring, it is, e.g. phenyl unsubstituted or substituted by one or more substituents chosen from C_1—C_6 alkyl, preferably methyl and tert-butyl; amino; nitro; halogen, preferably chlorine; trihalo-C_1—C_6 alkyl, preferably trifluoromethyl; C_1—C_4 alkoxycarbonyl, preferably —$COOCH_3$ and —$COOC_2H_5$; C_2—C_6 alkanoyl, preferably acetyl; C_2—C_7 acylamino, preferably acetylamino; and C_1—C_6 alkoxy.

When R_4 is a hetero-aromatic monocyclic ring, it is preferably pyridine.

When R_4 is a bicyclic ring, it is preferably quinoline. The skel ton of the β-lactam antibiotic referr d to above is preferably the skeleton of a penicillin, a cephalosporin, a penem, a carbapenem or a 1-oxa-1-dethiacephalosporin. Preferably E is —O— or —S—, especially —S—. Preferably the symbol  is a group chosen from:



wherein R_5 is hydrogen or an organic group; more preferably it is the

group, which completes with the fused azetidinone ring and the —E— group, when —S—, -a penem nucleus.

When R_5 is an organic group, it is, e.g., an unsubstituted or substituted C_1—C_4 alkyl group, preferably a methyl group unsubstituted or substituted by a substituent chosen from

a') halogen, e.g., chlorine or bromine;

b') an acyloxy group, e.g. a C_2—C_9 alkanoyloxy group, in particular acetoxy;

c') a carbamoyloxy group unsubstituted or substituted by one or two substituents chosen from C_1—C_4 alkyl and phenyl; and

d') a —S—Het group, wherein Het denotes a saturated or unsaturated, heteromonocyclic or heterobicyclic ring, containing one or more heteroatoms chosen from nitrogen, oxygen and sulphur. Said ring is, preferably, chosen from the group consisting of thiazole, thiadiazole, tetrazole, triazine and tetrazolo-pyridazine, and is in turn unsubstituted or substituted by one or more substituents chosen, e.g., from cyano; C_1—C_{12} alkyl, preferably C_1—C_4 alkyl; hydroxy; amino; halogen, preferably chlorine; C_1—C_{12} alkoxy, preferably C_1—C_4 alkoxy; formyloxy; C_2—C_{12} acyloxy; carboxy; C_1—C_{12} alkoxycarbonyl and carbamoyl unsubstituted or substituted by one or two C_1—C_4 alkyl group.

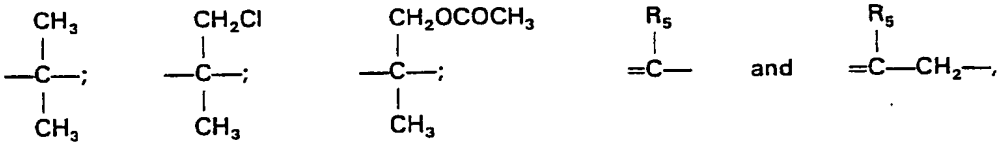
Preferred compounds of formula (I) are those wherein:

R_1 is hydrogen, chlorine, bromine, amino, phenylacetamido, phenoxyacetamido, 2-amino-2-phenyl-acetamido, 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido, C_1—C_4 alkyl or 1-hydroxyethyl;

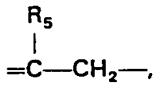
R_2 and R_3, being the same or different, are hydrogen or C_1—C_6 alkyl;

R_4 is phenyl, unsubstituted or substituted by 1, 2 or 3 substituents chosen from chlorine, nitro, methoxy, C_1—C_4 alkyl, amino, formamido, C_2—C_3 alkanoylamino;

X is oxygen; the symbol —E— represents —S— or —O—, wherein, when the symbol —E— represents —S—, the symbol —Y— represents a group chosen from:



wherein R_5 is as defined above and wherein, when the symbol —E— represents —O—, then the symbol —Y— represents



wherein R_5 is as defined above; and the salts thereof.

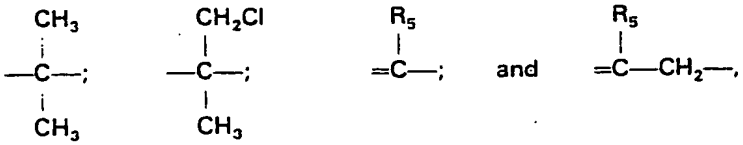
More preferred compounds of formula (I) are those wherein:

R_1 is hydrogen, chlorine, bromine, amino, phenylacetamido, phenoxyacetamido, 2-amino-2-phenyl-acetamido, 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido, C_1—C_4 alkyl or 1-hydroxyethyl;

R_2 and R_3 are hydrogen;

R_4 is phenyl, p-nitrophenyl, p-aminophenyl, p-chlorophenyl, p-tolyl, p-tert-butylphenyl, p-acetamidophenyl;

X is oxygen; the symbol E represents —S— or —O—, wherein, when the symbol —E— represents —S—, the symbol —Y— represents a group chosen from:



and wherein, when the symbol —E— represents —O—, the symbol - - Y represents

$$\begin{array}{l} R_5 \\ | \\ =C—CH_2—, \end{array}$$

wherein in both the cases R_5 is C_1—C_4 alkyl unsubstituted or substituted by a substituent chosen from:

a″) chlorine or bromine;

b″) a C_2—C_9 alkanoyloxy group;

c″) a carbamoyloxy group unsubstituted or substituted by one or two substituents chosen from C_1—C_4 alkyl and phenyl, and

d″) a —S—Het group, wherein Het denotes a heteromonocyclic or heterobicyclic ring chosen from the group consisting of thiazole, thiadiazole, tetrazole, triazine and tetrazolopyridazine, wherein said ring is in turn unsubstituted or substituted by 1, 2 or 3 substituents chosen from cyano, C_1—C_{12} alkyl, amino, bromine, chlorine, hydroxy, C_1—C_{12} alkoxy, formyloxy, C_2—C_{12} acyloxy, carboxy, C_1—C_{12} alkoxycarbonyl, and carbamoyl unsubstituted or substituted by one or two C_1—C_4 alkyl groups; and the salts thereof.

Particularly preferred compounds of formula (I) are those wherein:

R_1 is ethyl or 1-hydroxyethyl;

R_2 and R_3 are hydrogen;

R_4 is phenyl, p-nitrophenyl, p-aminophenyl, p-chlorophenyl; X is oxygen;

the symbol —E— is sulphur;

the symbol - - - Y - is a group

$$\begin{array}{l} R_5 \\ | \\ =C—, \end{array}$$

wherein R_5 is acetoxymethyl, carbamoyloxymethyl, (1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl, (1-carboxymethyl-1,2,3,4-tetrazol-5-yl)-thiomethyl, [1-(2-carboxy)ethyl-1,2,3,4-tetrazol-5-yl]-thiomethyl, 2-(2-methyl-5-oxo-6-hydroxy-2,5-dihydro-1,2,4-triazin-3-yl)-thiomethyl, [1-(2-dimethylamino)-ethyl-1,2,3,4-tetrazol-5-yl]-thiomethyl, and the salts thereof.

Salts of the compounds of formula (I) include acid addition salts either with inorganic, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric and phosphoric, acids, or organic, e.g. acetic propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic and salicylic, acids as well as salts either with inorganic, e.g. alkali metal, especially sodium or potassium bases, or alkaline-earth metal, especially calcium or magnesium bases, or with organic bases, e.g. alkylamines, preferably triethylamine.

It is well known that the removal of a conventional carboxy protecting group from a β-lactam derivative, especially from a bicyclic one, may be a critical reaction. The choice of a suitable ester, i.e. an ester which can safely survive through a multistep process, yet being readily cleaved at its end, is often the crucial factor in the success of a synthetic pathway leading to a compound of formula (I), no matter how trivial the former and how fascinating the latter may look; hence the constant need for new carboxy protecting groups in the chemistry of β-lactam antibiotics.

The esters of formula (I) and the salts thereof provide a new family of carboxy protecting groups, generally cleavable under the mild conditions required for the survival of the sensitive β-lactam moiety, with the additional advantage that the desired degree of reactivity can be modulated by the choice of the substituent(s) on the R_4 ring. More specifically, electron-withdrawing substituents (e.g., R_4=p-nitrophenyl) provide increased stability towards acid hydrolysis, while electron-donating substituents (e.g., R_4=p-methoxyphenyl) lessen the stability of esters (II) in comparison with the basic entry (R_4=phenyl).

The main advantage offered by the esters of formula (I) and salts thereof over the conventional carboxy protecting groups known in the literature and undor current use, as benzyl, p-nitrobenzyl, tert-butyl, diphenylmethyl or the like, lies in the mildness of the conditions needed for their cleavage.

Moreover, most of them are resistant to ozonolysis and cold aqueous permanganate, unlike, e.g. allyl esters, and the α-phosphoranylidene derivatives thereof can readily undergo an internal Wittig reaction with a thioester carbonyl of the type described by Woodward et al., J. Am. Chem. Soc., 100, 8214, 1978, unlike, e.g., trichloroethyl esters.

An eloquent example is offered by the synthesis of (5R,6S)-6-ethyl-2-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl-penem-3-carboxylic acid, which we were unable to achieve by catalytic hydrogenation of its benzyl or p-nitrobenzyl ester (reduction to the 2-methylpenem occuring instead), or by titration of its acetonyl ester with 0.1N NaOH (migration of the penem double bond to the exocyclic position), or by trifluoroacetic acid—or trim thylsilyliodide—mediated hydrolysis of its tert-butylester (loss of the β-lactam moiety). Eventually, said product was obtained in high yield, according to the present invention by extremely mild acid hydrolysis of its 1-phenoxyethylester, i.e. by simple

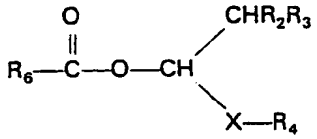
exposure to aqueous acetic acid or even by stirring with an aqueous solution of sodium metabisulphite.

Another advantage offer d by the esters of formula (I) and salts thereof, due to their possibility t survive through various processes yet being readily cleaved at their end, is th ir use in processes concerning the interconversion betwe n compounds of formula (I), which otherwise should not be possible or convenient to carry out on the corresponding free acids.

An additional advantage offered by the use of said esters and salts thereof is the easiness of the esterification of their carboxylic acid precursors, which does not require any activation step, such as their prior conversion into acyl halides. Another advantage over some of the known reagents used in the protection of carboxylic acids is their low cost, as the preparation (*vide infra*) of most of the esters of formula (I) can be achieved in bulk starting from extremely cheap materials, such as acetylene, phenol and hydrogen chloride. As is known, the free acids deriving from the cleavage of the esters of formula (I) have a high antibacterial activity both in animals and in humans against gram-positive and gram-negative bacteria such as straphylococci, streptococci, diplococci, *Kleibsiella, Escherichia coli, Proteus, mirabilis, Salmonella, Shigella, Haemophilus* and *Neisseria*. They show also a high activity against the strong betalactamase producer microorganisms, such as, for example, *Klebsiella aerogenes 1082 E, Escherichia coli Tem, Enterobacter cloacae P 99*, and indole-positive Proteus and the like, as well as against *Pseudomonas aeruginosa* strains. The said free acids and the pharmaceutically acceptable salts thereof are therefore useful in human therapy and in veterinary.

The compounds of formula (I) can be prepared by a process comprising:

A) joining a synthon of formula (II)

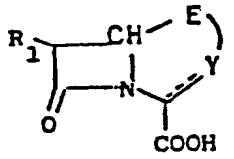


(II)

wherein

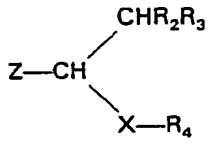
R_6 is a radical deriving from an α-aminoacid, an α-hydroxyacid, an α-ketoacid, or an α-alkenoic acid, wherein the amino, hydroxy and keto groups are either free or protected with a protective group in current use in the field of peptides, and

R_2, R_3, R_4 and X are as defined above, with another synthon and then processing the obtained intermediate product along known *per se* procedures to give a compound of formula (I); or B) reacting an acid of formula (III)



(III)

wherein the symbols —E—, ---Y and R_1 are as defined above, or a salt thereof, with a halide of formula (IV)



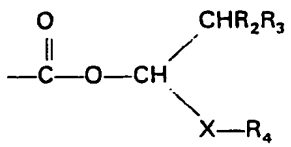
(IV)

wherein

Z is chlorine, bromine or fluorine and R_2, R_3, R_4 and X are as defined above; and, if desired, converting a compound of formula (I) into another compound of formula (I); and/or if desired converting a compound of formula (I) into a salt thereof; and/or, if desired obtaining a free compound of formula (I) from a salt thereof; and/or, if desired, separating a mixture of isomers of formula (I) into the single isomers.

The compounds of formula (I) can be converted into the corresponding free carboxylic acids by a new process, which is also included in the scope of the present invention.

The second synthon (or building block) used in process A) given above may be any fragment which can be located in the structure of the compound of formula (I) as long as it does not contain the ester group

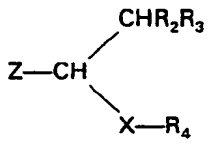


which is already provided in process A) by the synthon of formula (II). Normally, the product of the reaction between the synthon of formula (II) and the second synthon, will be a compound to be further processed.

The preparation of a synthon of formula (II) comprises reacting a carboxylic acid of formula (V)

$$R_6—COOH \qquad (V)$$

wherein R_6 is as defined above, or a salt thereof, with a halide of formula (IV)



(IV)

wherein

Z, R_2, R_3, R_4 and X are as defined above.

The method, reported above under A), comprises processing the product of formula (II) according to general methods known *per se* to afford a conventional ester of an acid of formula (III) (e.g., the p-nitrobenzyl ester thereof starting from a conventional ester of an acid of formula (V). Among these methods, preferred procedures are those which allow the multistep conversion of an ester of glyoxylic acid, i.e. a compound of formula (V) wherein R_6 is HCO; into a penem (see, among others, Woodward et al., J. Am. Chem. Soc., *101*, 6296, 1979).

A number of other procedures are depicted, for example, by R. Bucourt in "Recent Advances in the Chemistry of β-Lactam Antibiotics", Royal Soc. of Chemistry, Special Publ. no. 38 (1980), 1—25.

According to a preferred procedure of the invention, the carboxylic acid of formula (V) is preferably chosen from the group consisting of tartaric, fumaric and glyoxylic acid.

The reaction between a compound of formula (V), or a salt thereof, and a compound of formula (IV) may be carried out in an inert organic solvent, e.g., dimethylformamide, dimethylsulphoxide, tetrahydrofuran or acetone, at a temperature range between about —70°C and about 140°C, preferably between about —20°C and about 50°C. When a compound of formula (V) is used as free acid, the presence of an added organic or inorganic base is usually required.

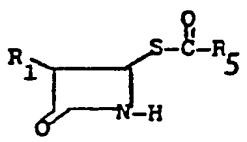
Suitable organic bases are, for instance, pyridine, lutidine, collidine or an aliphatic tertiary amine, such as triethylamine or ethyldiisopropylamine; suitable inorganic bases are, for example, alkali metal or alkaline earth hydroxides, e.g., NaOH; carbonates or hydrogen carbonates. Said bases are preferably used in approximately one molar equivalent amount.

Among all the procedures known *per se* regarding the process reported above under A), a preferred one starts from a compound of formula (II) and leads to a compound of formula (I), wherein the symbol —E— is sulphur and the symbol is

wherein R_5 is as defined above. Said preferred procedure comprises

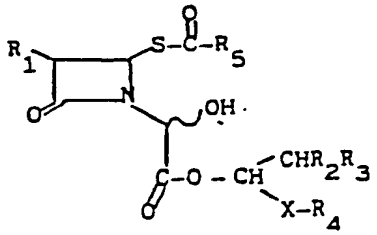
1') oxidizing a compound of formula (II), wherein R_6 represents the radical deriving from the L(+)tartaric acid, to give a compound of formula (II), wherein R_6 is formyl;

2') condensing said compound, or a hydrate, an acetal or hemiacetal thereof, with an azetidinone of formula (VI)



(VI)

wherein R_1 and R_5 are as defined above, to obtain a compound of formula (VII)

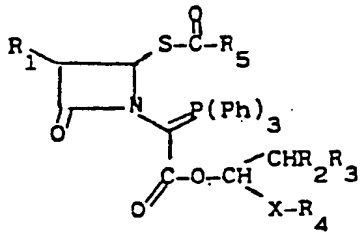


(VII)

wherein

R_1, R_2, R_3, R_4, R_5 and X are as defined above;

3') converting a compound of formula (VII) into a compound of formula (VIII)



(VIII)

wherein

R_1, R_2, R_3, R_4, R_5 and X are as defined above and Ph represents phenyl; and

4') cyclizing a compound of formula (VIII) to obtain a compound of formula (I), wherein the symbol —E— represents —S— and the symbol - - - Y represents

wherein R_5 is as defined above.

The step depicted above under 1') may be carried out with a suitable oxidizing agent, e.g., lead tetracetate.

The steps depicted above under 2'), 3') and 4') may be performed according to well known procedures, for example, those reported in our published British Patent Application No. 8005476.

In particular, for instance, step 2') may be carried out A) by heating in an anhydrous inert solvent, such as benzene or toluene, with simultaneous azeotropic distillation of the water formed, or B) by treatment with molecular sieves at room temperature, or C) in an aprotic dipolar solvent, such as tetrahydrofuran, in the presence of a basic catalyst such as triethylamine, at a temperature from room temperature to the boiling point of the solvent used. Step 3') may, for instance, be carried out by reacting the compound of formula (VII) with a halogenating agent to give the corresponding halide (preferably halogenation is carried out with thionylchloride to give the chloride), and then reacting the resulting halide with triphenylphosphine, either at room temperature on an inert support, i.e. in the absence of a solvent, or in an inert organic solvent, e.g. dichloromethane, tetrahydrofuran or dioxane, at a temperature from room temperature to about 70°C. Step 4') may, for example, be carried out by heating in an inert solvent, e.g. benzene, toluene, tetrahydrofuran dioxane or dichloromethane, at temperatures varying from about 70°C to about 150°C, preferably operating under nitrogen atmosphere.

The reaction between a compound of formula (III) and a compound of formula (IV) may be carried out under the same experimental conditions reported above for the reaction between a compound of formula (V) and a compound of formula (IV).

As stated above, a compound of formula (I) may be converted into another compound of formula (I), differing in one or both the meanings of R_1 and Y, to be chosen among the ones already stated.

When a conversion of this type concerns the R_1 group it may be, for example, the conversion of a protected amino into a free amino, and/or the conversion of a free amino into an acylamino, or a conversion of an alkyl group carrying a protected hydroxy into an alkyl group carrying a free hydroxy substituent. When a conversion of this type concerns the Y radical, it may be, for example, the chemical modification of a substituent in the position 3 of a cephalosporin, or of a 2-thiacephem, or the chemical modification of a substituent in position 2 of a penem, or of a penam. Alternatively, the E and Y radicals may be modified to such a degree to complete, after said conversion, a bicyclic β-lactam nucleus different from the starting one, to be chosen between the penicillin, cephalosporin, penem, carbapenem or 1-oxa-1-dethiacephalosporin classes, a familiar example of this type of conversion being the ring enlargement from a penicillin into a cephalosporin.

Said conversions are processes known *per se* and may be carried out by analogy with well known procedures, for example under the same experimental conditions already reported in the literature for the conversion of a conventional ester, e.g. p-nitrobenzyl ester, of an acid of formula (III) into the same conventional ester of a different acid of formula (III).

The optional salification of a compound of formula (I) as well as the conversion of a salt into free compound and the separation of a mixture of isomers into the free compound and the may be carried out by conventional methods.

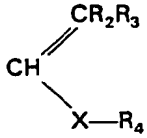
For example the separation of optical isomers may be carried out by salification with an optically active base or acid and by subsequent fractional crystallization of the diastereoisomeric salts following by recovering of the optically active isomeric acids or, respectively, bases. The separation of a mixture

of *cis*- and *trans*-geometric isomers may be carried out for example by fractional crystallization or by chromatography.

The preparation of a free acid of formula (III) from an ester of formula (I), which is also included in the scope of the present invention, is performed by cleavage of the ester of formula (I). The cleavag is preferably carried out by hydrolysis, preferably acid hydrolysis. The acid hydrolysis normally encompasses the use of a variety of Lewis and Bronsted acids, mainly depending upon the group R_4 present in the starting ester.

Selected hydrolysis conditions with Bronsted acids include trifluoroacetic acid, diluted in an inert organic solvent or neat (suitable, for example, when R_4 is a phenyl ring substituted with electron-withdrawing groups, such as NO_2); p-toluenesulphonic acid in benzene (1—2 hours at room temperature are generally enough when R_4 is unsubstituted phenyl); formic acid. Weaker inorganic (e.g., boric acid) or carboxylic acids (e.g. citric acid, oxalic acid, acetic acid, phthalic acid), usually dissolved in a mixture of water and an organic solvent, e.g. tetrahydrofuran, are preferably employed with the more sensitive β-lactam substrates. Even a solution of $Na_2S_2O_5$ in a mixture of water and an organic solvent, or a slightly acidic aqueous buffer can be often used when R_4 does not contain electron-withdrawing substituents, while esters of formula (I) wherein R_4 is a phenyl ring substituted by electron-donating groups (e.g., OCH_3) can be cleaved by simple exposure to water. Selected Lewis acids which can mediate the cleavage of esters of formula (I) are, for example, $AlCl_3$, BF_3, $ZnBR_2$, $ZnCl_2$, $SnCl_4$, $FeCl_3$. They can be used in an inert organic solvent, for example dichloromethane or nitromethane, or in a mixture of organic solvents, usually at a temperature varying from about —20°C to about +30°C, preferably around 0°C, again the more reactive Lewis acids (e.g., $AlCl_3$) being necessary when R_4 contains electron-withdrawing substituents, and less reactive ones (e.g., $ZnCl_2$) being preferred otherwise. In the particular instance of R_4 representing o- or p-nitrophenyl, cleavage of the ester may be mediated by chemical (e.g., NH_4Cl/iron powder) or catalytic reduction (e.g., hydrogen/Pd on charcoal), since the cleavage of the intermediate esters of formula (I) wherein R_4 is o- or p-aminophenyl is even easier.

Halides of formula (IV) may be prepared by addition of an acid of formula HZ_n, wherein Z is as above defined, to a vinyl ether/thioether of formula (IX)



(IX)

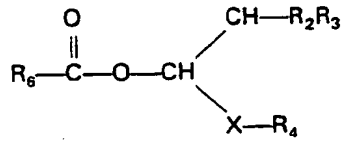
wherein R_2, R_3, R_4 and X are as above defined. Said reaction may be performed in or without the presence of an inert, dry organic solvent, such as, for example, tetrahydrofuran, preferably in the absence of water or a moisture, and at a temperature range between about —50°C and about +50°C, preferably between about —15°C and about +30°C.

Compounds of formula (IX) are known compounds or may be prepared starting from known compounds according to general methods.

Selected typical methods include the addition of a phenol/thiophenol to an alkyne (see, for example, W. Reppe et al., Annalen der Chemie *601*, 81, 1965); the reaction of a vinyl halide (e.g., vinyl chloride) or of a vinyl ester (e.g., vinyl acetate) with a phenol/thiophenol; the reaction of an alkyl-aryl ether/thioether, substituted on position 2 of the alkyl chain with a suitable leaving group (e.g., a halide, a mesyloxy group), with a base (see, among others, W. M. Lauer and M. A. Spielman, J. Am. Chem. Soc., *55*, 1572, 1933).

Compounds of formula (III), (V) and (VI) are known compounds or may be prepared by known methods from known compounds.

The invention provides also compounds having formula (II)



(II)

wherein

R_6 is a radical deriving from an α-aminoacid, an α-hydroxyacid, an α-ketoacid, or an α-alkenoic acid, wherein the amino, hydroxy and keto groups are either free or protected with a protective group in current use in the field of peptides and R_2, R_3, R_4 and X are as defined above.

Preferred compounds of formula (II) are those wherein

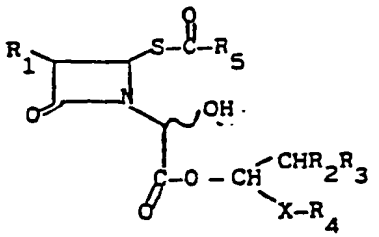
R_2 and R_3 are hydrogen;

R_4 is phenyl, p-nitrophenyl, p-chlorophenyl, p-aminoph nyl, p-tolyl, p-tert-butylphenyl, p-acetamidophenyl;

X is xygen;

R_6 is the radical deriving from the tartaric or fumaric or glyoxylic acid.

The invention provides also compounds having formula (VII)

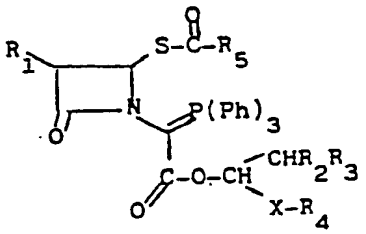


(VII)

wherein

R_1, R_2, R_3, R_4, R_5 and X are as defined above.

The invention provides also compounds having formula (VIII)



(VIII)

wherein

R_1, R_2, R_3, R_4, R_5, X and Ph are as defined above.

Particularly preferred compounds of formula (VII) and (VIII) are those wherein

R_1 is ethyl or 1-hydroxyethyl;

R_2 and R_3 are hydrogen;

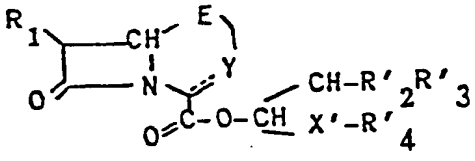
X is oxygen;

R_4 is phenyl, p-nitrophenyl, p-chlorophenyl, p-aminophenyl, p-tolyl, p-tert-butylphenyl, p-acetamidophenyl;

R_5 is acetoxymethyl, carbamoyloxymethyl, (1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl, [1-(2-dimethylamino)-ethyl-1,2,3,4-tetrazol-5-yl]-thiomethyl, (1-carboxymethyl-1,2,3,4-tetrazol-5-yl)-thiomethyl, [1-(2-carboxy)-ethyl-1,2,3,4-tetrazol-5-yl]-thiomethyl, 2-(2-methyl-5-oxo-6-hydroxy-2,5-dihydro-1,2,4-triazin-3-yl)-thiomethyl.

As stated above, the compounds of formula (I), besides being useful in various chemical processes as reported before, can be easily hydrolyzed to give the free carboxylic acids of formula (III) reported above. As already said, the acids of formula (III), and their pharmaceutically or veterinarily acceptable salts, are provided with high, broad-spectrum antibacterial activity against most of Gram-positive and Gram-negative bacteria, both in animals and in humans, and are therefore useful in the treatment of the infections caused by said microorganisms to humans and animals, such as respiratory tract infections, e.g. bronchitis, bronchopneumonia, pleurisy; hepatobiliary and abdominal infections, e.g. pyelonephritis, cystitis; obstetrical and gynecological infections, e.g. cervicitis, endometritis; ear nose and throat infections, e.g. otitis, sinusitis, parotitis.

The invention provides also, as useful compounds owning antibacterial activity, compounds of the following formula (Ia)



(Ia)

wherein R_1, —E— and the symbol  are as defined above; R'_2 and R'_3 are both hydrogen; X' is oxygen; and R'_4 is phenyl, 4-methylphenyl, 4-chlorophenyl, 4-acetamidophenyl and 4-methoxyphenyl, and the pharmaceutically or veterinarily acceptable salts thereof, as well as the pharmaceutical or veterinary compositions containing a compound of formula (Ia) or a salt thereof as the active principle.

The toxicity of the compounds of formula (Ia) was found to be similar to that of the corresponding free carboxylic acids of formula (III), and therefore they can be safely used in therapy.

The compounds of formula (Ia) can be administered to mammals at dosage levels similar to those adopted for the corresponding free carboxylic acids of formula (III). The compounds of formula (Ia) are preferably administered orally, although they may be administered also in other conventional ways, for example parenterally, e.g. by intramuscular or intravenous injections, or by rectal way. When the compounds of formula (Ia) are, for example, penems, the dosage levels for the oral administration in

adult humans range from about 100 mg to about 200 mg per dose, 1 to 4 times a day, the exact dosage level depending on the age, weight and conditions of the patient.

As stated above, the scope of the invention includes also a pharmaceutical or veterinary composition comprising a compound of formula (Ia) or a salt thereof in association with a pharmaceutically or veterinarily acceptable excipient (which can be a carrier or diluent).

The pharmaceutical or veterinary compositions containing the compounds of formula (Ia) or a salt thereof are usually prepared by following conventional methods and are administered in a pharmaceutically or veterinary suitable form.

The pharmaceutical forms used for the oral administration may be, for example, tablets, capsules, sugar or film coated tablets, liquid dispersions. The pharmaceutical forms used for the parenteral, e.g. intramuscular or intravenous administration may be, for example solutions or suspensions: for intramuscular injections suspensions or solutions, for intravenous injections aqueous solutions may be used.

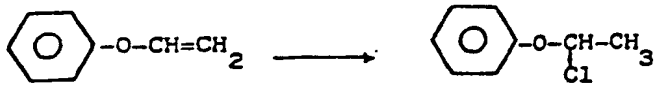
The pharmaceutical forms used for the rectal administration may be, for example, suppositories. The pharmaceutical forms contain the compounds of formula (Ia) and a pharmaceutically acceptable carrier and/or a pharmaceutical acceptable diluent.

The solid oral forms may contain, together with the active compound, diluents, e.g., lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl cellulose, polyvinyl pyrrolidone; disaggregating agents, e.g. a starch or alginic acid. The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions. The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol. The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspensions or solutions for intramuscular injections may contain together with the active compound a pharmaceutically acceptable carrier, e.g. sterile isotonic water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin. The following Examples illustrate but don't limit the invention.

Example 1
1-Phenoxy-1-chloro-ethane

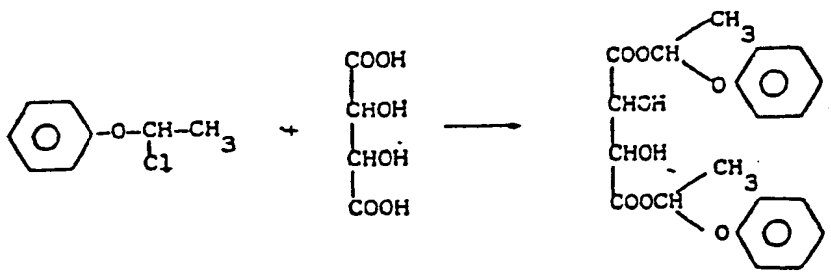


Anhydrous hydrogen chloride was passed through neat phenylvinyl-ether (26.5 g, 0.22 mol) at 0°C under stirring until the theoretical amount was adsorbed (approx. 8 g). The mixture was purged with nitrogen, and the obtained product (34.3 g) was used as such for the following step.

NMR δppm ($CDCl_3$)

1.88 (3H, d, J=5.5 Hz, CH—CH_3)
6.08 (1H, q, J=5.5 Hz, CH—CH_3)
6.8—7.4 (5H, m, Ar)

Example 2
1-Phenoxyethyl tartrate



A solution of L(+) tartaric acid (16.1 g, 0.11 mol) and triethylamine (30.8 cc, 0.22 mol) in DMF (120 cc) was added dropwise in thirty minutes to an ice-cooled solution of 1-chloro-1-phenoxyethane (34.5 g, 0.22 mol) in DMF (80 cc).

A white precipitate formed in a few minutes.

After one hour the reaction mixture was pour d into ice-water (1:1, 500 g) with stirring, and then extracted three times with diethyl ether (3x200 cc).

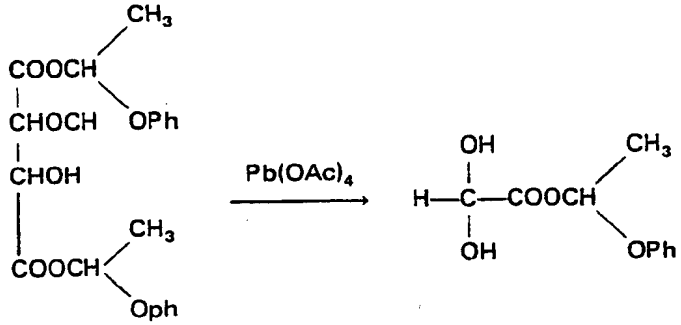
The combined organic phase was washed with 4% aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and evaporated, to give the title compound as a light yellow oil (42 g, 98%).

IR ν_{max} ($CHCl_3$) 3450, 3060, 2970, 2930, 1740, 1590, 1490, 1115 cm^{-1}

NMR δppm ($CDCl_3$)

1.62 and 1.64 (6H, each d, CH—*CH_3* and COOCH(Ph)*CH_3*)
4.43, 4.45, 4.59 and 4.60 (2H, each s, *CH*—OH)
6.53, 6.54, 6.62 and 6.64 (2H, each q, *CH*—CH_3)
6.8—7.26 (10H, m, Ar)

Example 3
1-Phenoxyethyl glyoxylate (hydrate)



Lead tetraacetate (46.1 g, 0.104 mol) was added portionwise under nitrogen to an ice-cold, stirred solution of 1-phenoxyethyl tartrate (38.3 g, 0.098 mol) in anhydrous tetrahydrofurn (250 ml).

A white precipitate formed immediately.

After one hour, the precipitate was filtered off and the filtrate was evaporated to give a brown oil which was dissolved in diethyl ether, sequentially washed with 4% aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), decolorized with charcoal and filtered over celite.

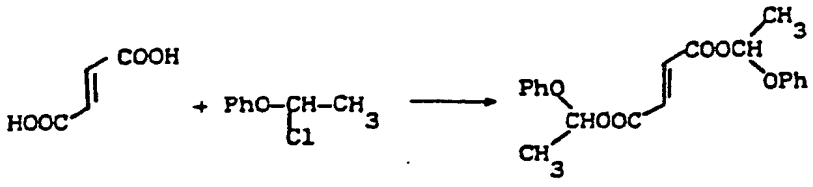
The filtrate was concentrated in vacuo to give a white slurry, which afforded the pure product upon crystallization from di-isopropyl ether; white crystals, m.p. 95—6°C (26.2 g, 63%).

IR ν_{max} ($CHCl_3$) 3540, 1745 cm^{-1}

NMR δppm ($CDCl_3/CD_3COCD_3$)

1.65 (3H, d, J=5.5 Hz, CH—*CH_3*)
5.23 (1H, dd, J=6.0 and 7.5 Hz, *CH*$(OH)_2$—)
5.52 (2H, m, exch. D_2O, CH(*OH*$)_2$)
6.58 (1H, q, *CH*—CH_3)
6.93—7.44 (5H, m, Ar)

Example 4
1-Phenoxyethyl fumarate



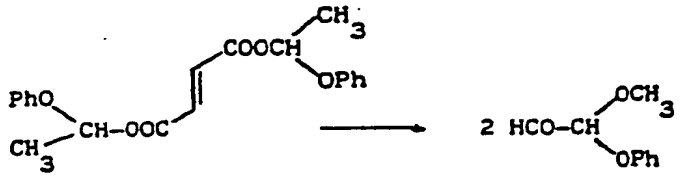
A solution of fumaric acid (8.7 g, 75 mmol) and triethylamine (21 ml, 150 mol) in dry dimethylformamide (30 ml) was treated at 0—10°C under stirring with a solution of 1-phenoxy-1-chloroethane (23.3 g, 150 mmol) in the same solvent (30 ml).

The reaction mixture was kept overnight in the refrigerator, after which time was poured into ice-water (200 ml) and extracted with ethyl ether. Evaporation of the solvent left the crude product which was crystallized from ethyl ether—light petrol to give white crystals, m.p. 87—88°C (16.1 g, 60%).

NMR δppm ($CDCl_3$)

1.60 (6H, d, J=5.5 Hz, CH—*CH_3*)
6.55 (2H, q, J=5.5 Hz, *CH*—CH_3)
6.7—7.3 (12H, m, vinyl and aryl protons)

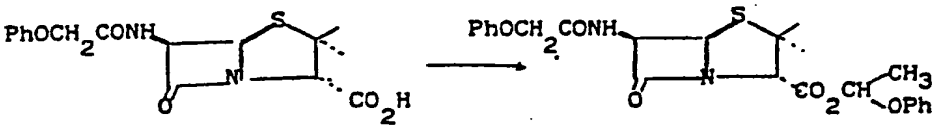
Exampl 5
1-Phenoxyethyl glyoxylate



A stream of ozone in dry oxygen was passed through a solution of 1-phenoxyethyl fumarate (0.6 g) in dichloromethane (20 ml) until a deep blue colour developed.

The solution was purged with nitrogen, and silica gel (2 g) was added. The mixture was let rise to room temperature under vigorous stirring and filtered after one hour. The filtrate was washed with dilute aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and evaporated, so obtaining the title product, identical with the sample described in Example 3.

Example 6
1-Phenoxyethyl 6-phenoxyacetamidopenicillanate

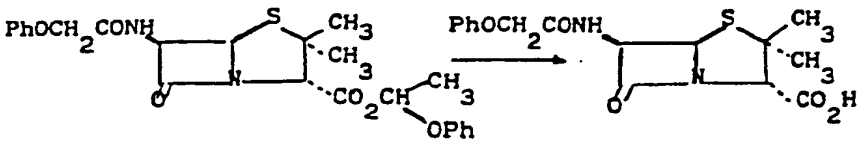


Triethylamine (200 μl, 1.43 mmol) was added to a solution of Penicillin V (500 mg, 1.43 mmol) in tetrahydrofuran (5 ml).

To this solution, 1-phenoxy-1-chloroethane (235 mg, 1.5 mmol) in acetonitrile (2 ml) was added at 0°C under stirring. After one hour at 0°C the reaction mixture was partitioned between ethyl ether and 4% aqueous $NaHCO_3$. Evaporation of the solvents from the dried (Na_2SO_4) organic layer left a syrup which was crystallized once from diisopropylether, thus obtaining the title product as a slightly waxy solid in almost quantitative yield.

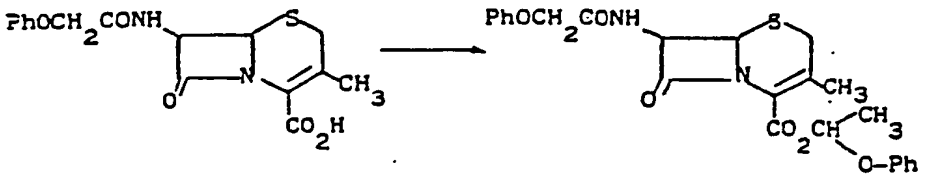
NMR δppm ($CDCl_3$)
1.29, 1.44, 1.50 and 1.57 (6H, each s, gem-CH_3)
1.68 (3H, d, J=5.5 Hz, CH—*CH_3*)
4.39 and 4.43 (1H, each s, N—CH—CO)
4.53 (2H, s, OCH_2—CO)
5.45—5.8 (2H, m, β-lactam protons)
6.63 (1H, m, *CH*—CH_3)
6.76—7.40 (11H, m, CONH and Ar)

Example 7
6-Phenoxyacetamidopenicillanic acid



A mixture of 1-hydroxyethyl 6-phenoxyacetamidopenicillanate (50 mg) and $ZnCl_2$ (58 mg) in dry, ethanol-free dichloromethane was stirred 30 min at room temperature. Ethyl acetate and 5% aqueous citric acid were then added and the organic layer was washed several times with brine, dried (Na_2SO_4), filtered over Hi-flow and evaporated, thus obtaining the anticipated Pencillin V as a white foam in almost quantitative yield.

Example 8
1-Ph noxyethyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate



A solution of 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylic acid (1.04 g, 3 mmol) and triethylamine (0.42 ml, 3 mmol) in cold (0°C) acetonitrile (5 ml) was added to a stirred solution of 1-chloro-1-phenoxyethane (0.47 g, 3 mmol) in the same solvent.

A white precipitate immediately formed.

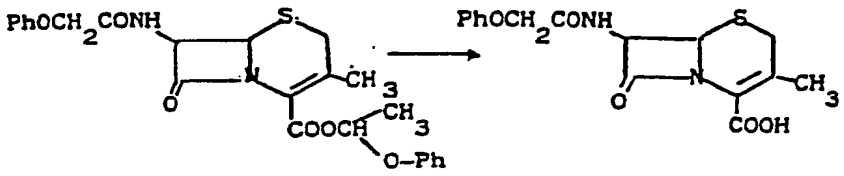
After 1 hour at 0°C, the reaction mixture was poured into ice-water and extracted with ethyl ether (2×50 ml). The organic extracts were dreid (Na_2SO_4) and evaporated to give the crude product as a solid in quantitative yield. An analitical sample was obtained by crystallization from ethyl ether; m.p. 90°C.

IR ν_{max} (KBr) 3430—3270, 1780, 1715, 1650, 1600, 1580 and 1525 cm^{-1}

NMR δppm ($CDCl_3$)

1.71 (3H, d, J=5 Hz, CH—*CH_3*)
2.03 (3H, br s, 3—CH_3)
3.33 (2H, ABq, J=18 Hz, separation of inner lines 14 Hz, 2—CH_2)
4.55 (2H, s, O—CH_2CO)
4.98 (1H, d, J=6 Hz, 6—H)
5.87 (1H, dd, J=6 and 9 Hz, 7—H)
6.69 (1H, q, J=5 Hz, *CH*—CH_3)
6.8—7.4 (11H, m, CONH and Ar)

Example 9
7-Phenoxyacetamido-3-methyl-3-cephem-4-carboxylic acid



Procedure a)

1-Phenoxyethyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (50 mg) was dissolved in 3.5 ml of a 20% trifluoroacetic acid solution in dry dichloromethane.

The mixture was stirred for 1 hour at −10°C.

Work-up (evaporation to dryness, partition of the residue between ethyl acetate and diluted aqueous $NaHCO_3$ solution, acidification of the latter and back-extraction with ethyl acetate) afforded the title product in almost quantitative yield.

Procedure b)

The 1-phenoxyethyl ester (48 mg) was dissolved in dry benzene (3 ml) and stirred for 1.5 hours at room temperature with a molar equivalent amount of p-toluenesulphonic acid (10 mg), after which time t.l.c. showed complete conversion. The mixture was filtered to collect a powder, 37 mg (quantitative yield), identical by t.l.c. with an authentic sample of the title product.

Procedure c)

1-Phenoxyethyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (50 mg) in dry dichloromethane (2 ml) was stirred with $ZnCl_2$ (58.2 mg) for 15 min at room temperature, after which time t.l.c. showed complete conversion. The reaction mixture was taken up in ethyl acetate, washed with diluted HCl solution, dried (Na_2SO_4) and evaporated to afford the title product.

Procedure d)

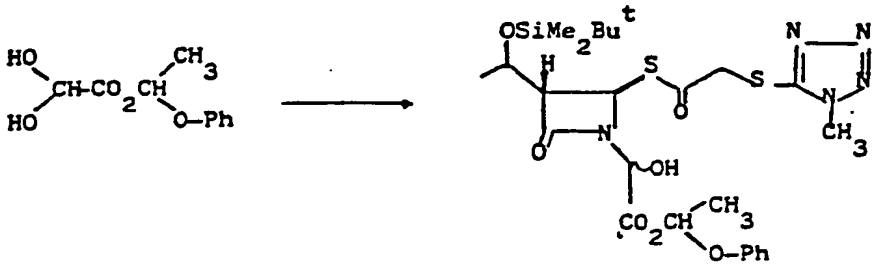
The 1-phenoxyethyl est r (50 mg) in dimethylformamide (1 ml) was treatd with 0.1 M aqueous $Na_2S_2O_5$ (1 ml).

After 16 hours stirring at room temperature, conversion to the title product was about 5%. Acetic acid (1 ml) was then added, the conversion rose to 45—50% after 24 hours.

When 0.1 ml H_3PO_4 85% was added, 80—85% conversion to the title product was observed by t.l.c. monitoring within 2 hours.

Example 10

3(S)-[1-(*R*)-tert-butyldimethylsilyoxyethyl]-4(*R*)-(1-methyl-1,2,3,4-tetrazol-5-yl)-thioacetylthio-1-[1-hydroxy-1-(1-phenoxyethyl) oxycarbonyl]-methyl-azetidin-2-one



Step a)

Bromoacetic acid (13.9 g, 0.1 mol) and sodium hydrogen carbonate (8.4 g, 0.1 mol) in water (100 ml) were added to 1-methyl-5-mercapto-tetrazole sodium salt (17.14 g, (0.1 mol) in 95% ethanol (100 ml), and the resulting mixture was stirred for 2 hours at room temperature. The organic solvent was removed *in vacuo*, the resulting aqueous solution was made acid with 2N HCl, saturated with NaCl and extracted several times with ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated to a slurry which crystallized from di-isopropyl ether, thus yielding 16.4 g (94%) of (1-methyl-1,2,3,4-tetrazol-5-yl)-thioacetic acid as white crystals, m.p. 112°C.

NMR δppm (d_6-acetone)
4.03 (3H, S, CH_3)
4.19 (2H, s, CH_2)
10.70 (1H, s, exch. D_2O, OH)

Step b)

A solution of the product from step a), 6.97 g, 0.04 mol) and triethylamine (0.56 ml, 0.04 mol) in dry dichloromethane (200 ml) was stirred for 5 min at 0°C, after which time PCl_5 (8.33 g, 0.04 mol) was added portionwise. After 30 min stirring at 0°C and an additional hour at room temperature, the mixture was evaporated to dryness *in vacuo*, taken up in dichloromethane (60 ml), filtered from the insoluble materials, and added dropwise to a solution of pyridine (12.9 ml. 0.16 mol) in dichloromethane (100 ml) which had been previously saturated with H_2S at 0°C. The resulting mixture was stirred for 70 min at 0°C, then freed from excess H_2S by evaporation *under vacuum*. The residue was dissolved in dichloromethane and sequentially washed with 10% H_2SO_4 and brine. Removal of the solvent left 7.5 g (quantitative yield) of (1-methyl-1,2,3,4-tetrazol-5-yl)-thioacetic acid.

IR ν_{max} (Nujol) 2540 and 1690 cm^{-1}
NMR δppm (d_6-acetone)
4.01 (3H, s, CH_3)
4.44 (2H, s, CH_2)
7.57 (1H, s, exch. D_2O, SH)

Step c)

A solution of the product from step b), (4.1 g, 21.6 mmol) in 1N NaOH (21.6 ml, 21.6 mmol) was added dropwise at 0°C to a solution of 3(*S*)-[1(*R*)-tert-butyldimethylsilyloxyethyl]-4-(*R,S*)-acetoxy-azetidin-2-one (4.1 g, 14.3 mmol) in water (40 ml) and acetone (80 ml).

The mixture was stirred for 2 hours at 10°C, occasionally adding a few drops of 1N NaOH in order to keep the pH between 7.6 and 7.9. Upon removal of the solvent the aqueous solution was extracted several times with dichloromethane, and the organic extracts were dried (Na_2SO_4) and evaporated in vacuo. Chromatography of the oily residue (SiO_2; EtOAc/C_6H_{12} as eluants) afforded 2.5 g (42%) of (3*S*)-[1(*R*)-tert-butyldimethylsilyloxyethyl]-4(*R*)-(1-methyl-1,2,3,4-tetrazol-5-yl)-thioacetylthio-azetidin-2-one as a colourless gum.

IR ν_{max} ($CHCl_3$) 1775 and 1690 cm^{-1}
NMR δppm ($CDCl_3$)
0.06 (6H, s, Me_2)
0.88 (9H, s, Bu^t)
1.20 (3H, d, J=6 Hz, CH_3—CH)
3.19 (1H, dd, J=2.0 and 4.0 Hz, CH—*CH*—CH)
4.01 (3H, s, N—CH_3)
4.25 (1H, m, CH_3—*CH*—CH)
4.39 (2H, s, CH_2)

5.34 (1H, d, J=2.0 Hz, CH—*CH*—S)
6.79 (1H, br s, exch. D_2O, NH)

Found: C, 43.32; H, 6.58; N, 16.67; S, 15.28
$C_{15}H_{27}N_5O_3SiS_2$ requires: C, 43.14; H, 6.52; N, 16.77; S, 15.36.

Step d)

A solution of the product from step c), 0.835 g, 2 mmol) and 1-phenoxyethyl glyoxylate hydrate (0.764 g, 3.6 mmol) in benzene was refluxed for 7 hours with azeotropic removal of the water formed during the reaction.

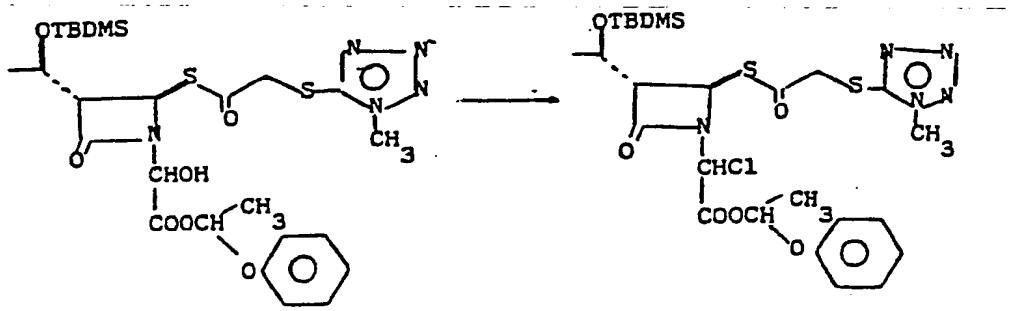
Chromatography (SiO_2; EtOAc/C_6H_{12} as eluants) of the residue afforded the title compound (mixture of four diastereoisomers) as a white foam (501 mg, 41%).

IR ν_{max} ($CHCl_3$) 3600—3100, 1765 and 1690 cm^{-1}

NMR δppm ($CDCl_3$)

0.06 (6H, s, Me_2)
0.87 (9H, s, Bu^t)
1.13 and 1.18 (3H, each d, CH_3—CH—OSi)
1.65 (3H, d, CH_3—CH—OPh)
3.00—3.40 (1H, m, CH—*CH*—CH)
3.92 (3H, s, N—CH_3)
4.10—4.30 (1H, m, CH_3—*CH*OSi)
4.15 and 4.28 (2H, each s, CH_2)
4.3—4.6 (1H, broad s, exch. D_2O, CH—*OH*)
5.20—5.35 (1H, m, CH—*CH*—S)
5.40—5.60 (1H, m, *CH*—OH)
6.30—6.70 (1H, m, CH_3—*CH*—OPh)
6.80—7.40 (5H, m, Ar)

Example 11
(4R)-(1-methyl-1,2,3,4-tetrazol-5-yl) thioacetylthio-(3S)-[(1R) tert-butyldimethylsilyloxyethyl]-1-[1-chloro-1-(1-phenoxethyl) oxycarbonyl] methyl-azetidin-2-one



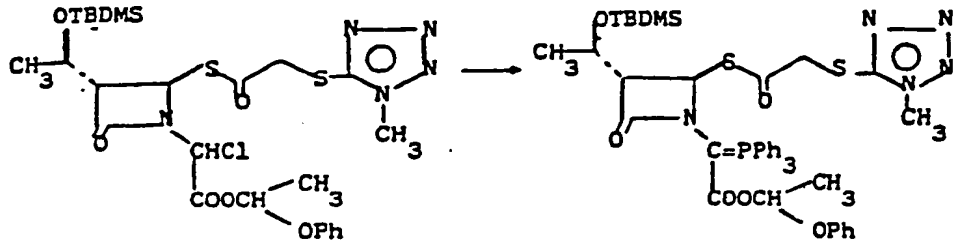
A stirred solution of (4R)-(1-methyl-1,2,3,4-tetrazol-5-yl) thioacetylthio-(3S)-[(1R) tert-butyldimethylsilyloxyethyl]-1-[1-hydroxy-1-(1-phenoxyethyl) oxycarbonyl] methyl-azetidin-2-one (360 mg; 0.59 mmol) in dry tetrahydrofuran (8 ml) at —35°C under nitrogen was sequentially treated with pyridine (0.05 ml; 0.62 mmol) and thionyl chloride (0.043 ml; 0.59 mmol).

A white precipitate formed immediately. After five minutes the reaction mixture was warmed up to 0°C, filtered and the solid washed with dry tetrahydrofuran.

The filtrate and the washings were evaporated to dryness in vacuo to give the crude title compound as a light yellow gum (370 mg; 100%).

IR ν_{max} ($CHCl_3$) 1785, 1700 cm^{-1}.

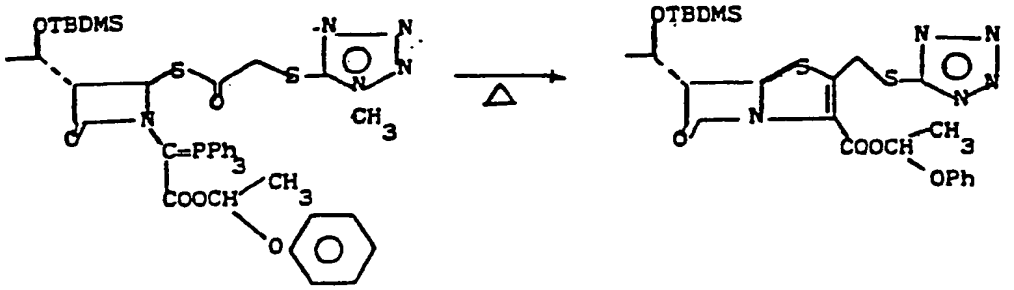
Exampl 12
(4R)-(1-methyl-1,2,3,4-tetrazol-5-yl)-thioacetylthio-(3S)-[(1R)tert-butyldimethylsilyl xyethyl]-1-[1-triphenylphosph ranyliden-1-(1-phenoxyethyl) xycarbonyl] m thyl-azetidin-2-one



To a solution of (4R)-(1-methyl-1,2,3,4-tetrazol-5-yl)-thioacetylthio-(3S)-[(1R) tert-butyldimethylsilyloxyethyl]-1-[1-chloro-1-(1-phenoxyethyl) oxycarbonyl] methyl azetidin-2-one (360 mg; 0.57 mmol), pyridine (0.046 ml; 0.57 mmol), triphenylphosphine (300 mg; 1.14 mmol) and silica gel (Kieselgel 60, 230—400 mesh; 2.2 g) were added with stirring. The solvent was thoroughly removed *in vacuo* and the residue was let stand for two hours at room temperature, after which time was put on the top of a silica gel column. Elution with ethyl acetate/cyclohexane mixtures gave the title compound as a white foam (283 mg, 58%).

IR ν_{max} ($CHCl_3$ 1755, 1690, 1620 cm^{-1}

Example 13
1-Phenoxyethyl (5R,6S)-6-[(1R)-tert-butyldimethylsilyloxyethyl]2-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl-penem-3-carboxylate



A solution of (4*R*)-(1-methyl-1,2,3,4-tetrazol-5-yl) thioacetylthio-(3S)-[(1R) tert-butyldimethylsilyloxyethyl]-1-[1-triphenylphosphoranyliden-1-(1-phenoxyethyl) oxycarbonyl]methyl-azetidin-2-one (282 mg; 0.33 mmol) in dry toluene (12 ml) was refluxed under nitrogen for three hours.

Removal of the solvent and chromatography on silica gel (ethyl acetate/toluene mixtures as eluants) afforded the title compound (two diastereo-isomers) as a gum; 120 mg, 63%.

UV λ_{max} (hexane) 334 nm

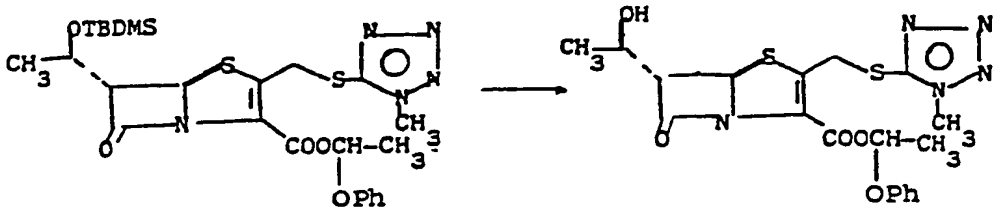
IR ν_{max} ($CHCl_3$) 1790, 1705 cm^{-1}

NMR δppm ($CDCl_3$)

0.05 (6H, s, Me_2)
0.87 (9H, s, Bu^t)
1.19 (3H, d, J=6 Hz, CH_3—CH—OSi)
1.68 (3H, d, J=5 Hz, CH_3—CH—OPh)
3.68 (1H, dd, J=2 and 4 Hz, CH—*CH*—CH)
3.88 (3H, s, N—CH_3)
4.21 (1H, m, CH_3—*CH*—OSi)
4.58 and 4.64 (2H, each ABq, J=13 Hz, separation of inner lines 14 and 7 Hz)
5.54 (1H, d, J=2 Hz, CH—*CH*—S)
6.58 and 6.63 (1H, each q, J=5 Hz, CH_3—*CH*—OPh)
6.90—7.40 (5H, m, Ar)

Found: C, 51.63; H, 6.24; N, 12.08; S, 10.88.
$C_{22}H_{35}N_5O_5SiS_2$ requires: C, 51.97; H, 6.11; N, 12.12; S, 11.10.

Example 14
1-Phenoxyethyl (5*R*,6*S*)-6-[1(*R*)-hydroxyethyl[-2-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl-3-pen m-3-carboxylate



Method A

A solution of 1-phenoxyethyl (5*R*,6*S*)-6-[1(*R*)-tert-butyldimethylsilyloxyethyl]-2-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethylpenem-3-carboxylate (22 mg; 0.038 mmol) in tetrahydrofuran (1 ml), water (1 ml) and acetic acid (3 ml) was stirred at 28°C for 5 hours.

The mixture was concentrated in vacuo.

Chromatography of the residue on silica gel eluting with ethyl acetate/toluene mixtures afforded first unreacted starting material and then the title compound as a white foam (4.6 mg; 26%).

UV λ_{max} (EtOH 95%)
332 nm

Method B

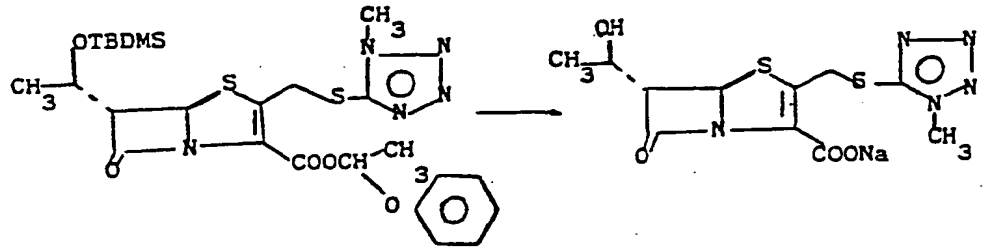
A solution of the o-silylated penem ester (15 mg; 0.026 mmol) in dry THF (0.5 ml) was treated with tetrabutylammonium fluoride (20.4 mg; 0.078 mmol) at 0°C. The resulting mixture was stirred for three hours at room temperature, then poured in water and extracted with ethyl acetate.

The combined organic phase was dried (Na_2SO_4) and evaporated to give a brown oil.

Chromatography on silica gel eluting with ethyl acetate/cyclohexane mixtures gave the title compound as a light yellow gum. (1.8 mg; 15%).

UV λ_{max} (EtOH 95%)
332 nm

Example 15
Sodium (5*R*,6*S*)-6-[1(*R*)-hydroxyethyl]-2-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl-penem-3-carboxylate



Procedure a)

A solution of 1-phenoxyethyl (5*R*,6*s*)-6-[1-(*R*)-tert-butyldimethylsilyloxyethyl]-2-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl-penem-3-carboxylate (69 mg; 0.12 mmol) in 0.4N aqueous oxalic acid (16 ml) and tetrahydrofuran (6 ml) was stirred for twenty hours at 25°C. The mixture was neutralized with $NaHCO_3$, evaporated to small volume in vacuo and then passed through a reverse phase column, eluting with water, thus obtaining the title compound as an amorphous solid (8 mg; 18%).

UV λ_{max} (H_2O)
315 nm

NMR δppm (D_2O)
1.28 (3H, d, J=6.3 Hz)
3.87 (1H, dd, J=1.4 and 6.3 Hz)
4.10 (3H, s)
4.19 (1H, m)
4.40 (2H, ABq, J=16.0 Hz, separation of inner lines 13 Hz)
5.59 (1H, d, J=1.4 Hz)

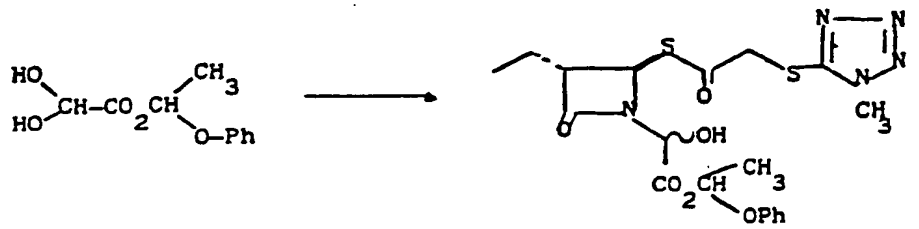
Procedure b)

The 1-phenoxyethyl penemcarboxylate (22 mg; 0.038 mmol) was dissolved in a 4:2:1 mixture of acetic acid/tetrahydrofuran/water and stirred for 16 hours at room temperature. T.L.C. showed more

than 80% conversion. The mixture was made neutral with $NaHCO_3$, concentrated and passed through a reverse-phas column to give the title product in 48% yield.

Example 16

(±)(3,4-Trans)-4-(1-methyl-1,2,3,4-tetrazol-5-yl) thioacetylthio-3-ethyl-1-[1-hydroxy-1-(1-phenoxyethyl)-oxycarbonyl]-methylazetidin-2-one



Step a)

(1-methyl-1,2,3,4-tetrazol-5-yl)-thioacetic thioacid (3 g, 15.8 mmol), prepared as described in Example 10, steps a—b, was allowed to react with (±)*trans* 4-acetoxy-3-ethylazetidin-2-one (1.57 g, 10 mmol) and 1N NaOH (15.8 ml) in water/acetone.

When the starting material had virtually disappeared, the mixture was partitioned between dichloromethane and water, and the organic extracts were evaporated to give a syrup which was purified by silica gel chromatography, thus affording 1.13 g of (±)(3,4-trans)-4-(1-methyl-1,2,3,4-tetrazol-5-yl)-thioacetylthio-3-ethyl-azetidin-2-one as a powder.

NMR δppm ($CDCl_3$)

1.04 (3H, t, J=5.0 Hz, CH_3—CH_2)
1.84 (2H, m, CH_3—CH_2—CH)
3.21 (1H, m, CH_2—CH—CH)
4.04 (3H, s, N—CH_3)
4.40 (2H, s, CH_2—S)
5.05 (1H, d, J=2.0 Hz, CH—CH—S)
7.13 (1H, br s, exch. with D_2O, NH)

Found:	C, 37.81; H, 4.42; N, 23.89; S, 22.28
$C_{19}H_{13}N_5O_2S$ requires:	C, 37.62; H, 4.56; N, 24.37; S, 22.32

Step b)

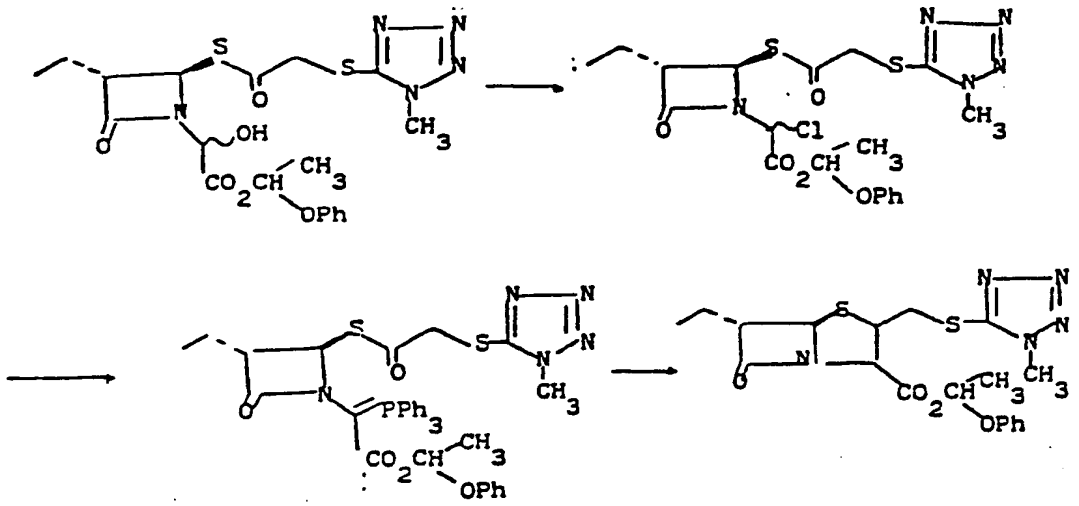
A solution of (±)(3,4-trans)-4-(1-methyl-1,2,3,4-tetrazol-5-yl)-thioacetylthio-3-ethyl-azetidin-2-one (1.1 g) and 1-phenoxyethyl glyoxylate hydrate (1 g) in benzene (25 ml) was refluxed for 5 hours in a Dean-Stark apparatus.

Complete removal of the solvent afforded the crude product, which could be isolated pure in 61% yield after silica gel chromatography as a mixture of diastereoisomers.

NMR δppm ($CDCl_3$)

1.02 (3H, t, CH_3—CH_2—)
1.67 and 1.73 (3H, each d, O—CH(OPh)CH_3)
1.80 (2H, q, CH_3CH_2—)
3.00—3.40 (1H, m, CH_2—CH—CH)
3.97, 3.98 and 3.99 (3H, each s, N—CH_3)
5.21, 5.23 and 5.31 (1H, each d, J=2.0 Hz, CH—CH—S)
5.38 (1H, m, N—CH—OH)
6.50, 6.62, 6.69 and 6.79 (1H, each q, OCH(OPh)CH_3)
6.90—7.50 (5H, m, Ar)

Example 17
(±)1-Phenoxyethyl (5,6-trans)-2-(1-methyl-1,2,3,4-tetraz l-5-yl)-thiomethyl-6-ethyl-penem-3-carboxylate



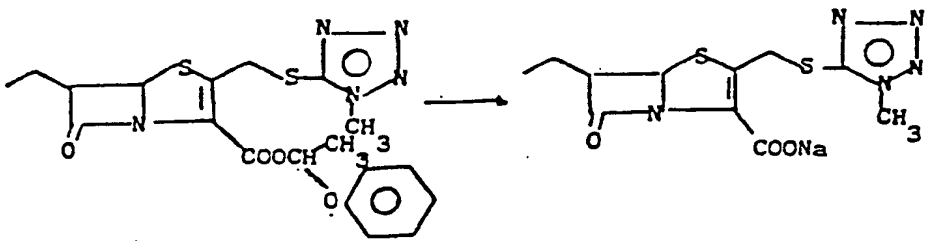
The title compound was obtained starting from (±)(3,4-trans)-4-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethylthio-3-ethyl-1-[1-hydroxy-1-(1-phenoxyethyl) oxycarbonyl]methyl-azetidin-2-one and following the same experimental procedure described in Examples 11, 12 and 13 (step I, 95%; step II, 63%; step III, 70% yield).

UV λ_{max} (CH_3OH)
332 nm

IR ν_{max} ($CHCl_3$)
1785, 1705 cm^{-1}

NMR δppm ($CDCl_3$)
1.05 (3H, t, J=7.0 Hz, CH_3—CH_2)
1.70 (2H, d, J=5.5 Hz, CH_3—CH)
1.81 (2H, m, CH_3—CH_2—CH)
3.84 (1H, m, CH_2—CH—CH)
3.91 (3H, s, N—CH_3)
4.47—4.82 (2H, each ABq, CH_2S)
5.39 and 5.41 (1H, d, J=2 Hz, CH—CH—S)
6.59 and 6.63 (1H, each q, J=5.5 Hz, OCH(OPh)CH_3)
6.90 and 7.40 (5H, m, Ar)

Example 18
(±)Sodium (5,6-trans)-2-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl-6-ethyl-penem-3-carboxylate



Procedure a)

(±)1-Phenoxyethyl (5,6-trans)-2-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl-6-ethyl-penem-3-carboxylate (44.8 mg; 0.1 mmol) was dissolved in dioxane (3 cc) and treated dropwise with a solution of 0.2N aqueous metabisulfite (3 cc). The mixture was vigorously stirred for 30 hours at 25°C.

The solution was concentrated to small volume and the pH adjusted at 7.0.

Chromatography on rev rse-phase column, eluting with water, afforded the title compound (Rf=0.32, THF/pH 7.4 1:1 phosphate buffer) as an amorphous solid (19.8 mg; 57%) and some unreacted starting material (5 mg).

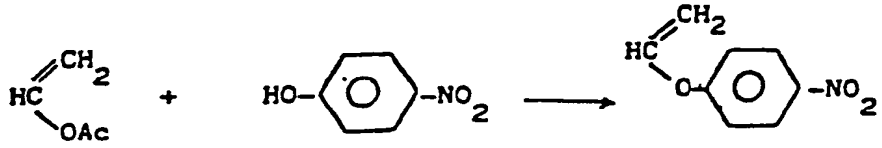
UV λ_{max} (H_2O)
314 nm

Procedure b)

The 1-phenoxyethyl penem carboxylate was stirred for several hours at room temperature in a mixture of acetic acid-tetrahydrofuran-water (4:2:1).

T.L.C. monitoring. Work-up and purification as described in Example 15 afforded the title compounds.

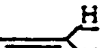
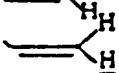
Example 19
p-Nitrophenyl-vinyl-ether



A mixture of p-nitrophenol (4.17 g, 30 mmol) and vinyl acetate (9 ml) in cyclohexane (9 ml) was stirred for 2 hours at room temperature in the presence of mercuric acetate (0.21 g) and 98% H_2SO_4 (2 drops). The reaction mixture was poured into ice cold 20% NaOH, and stirred for a few minutes. Ethyl ether was then added; the mixture was stirred again and the unreacted sodium p-nitrophenate was recovered by filtration.

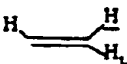
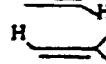
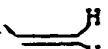
The organic layer was washed several times with water, dried (Na_2SO_4) and evaporated to give the title product (1—1.5 g).

An analitical sample was obtained by silica gel chromatography as a yellow powder.

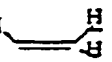
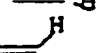
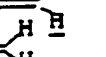
NMR δ ppm (d_6-acetone) 4.60 (1H, dd, J = 6 and 2 Hz, )
4.83 (1H, dd, J = 13 and 2 Hz, )
6.84 (1H, dd, J = 13 and 6 Hz, )
7.11 and 8.12 (4H, each d, J = 9 Hz, Ar)

By the same experimental procedure, and starting from the appropriate phenol, the following vinyl esters, among others, were obtained and characterized:

p-acetamidophenyl-vinyl ether

NMR δ_{ppm} ($CDCl_3$) 2.18 (3H, s, CH_3)
4.27 (1H, dd, J = 6 and 1.8 Hz, )
4.60 (1H, dd, J = 14 and 1.8 Hz, )
6.48 (1H, dd, J = 6 and 14 Hz, )
6.78 and 7.29 (4H, each d, J = 9 Hz, Ar)

p-tert-butylphenyl-vinyl-ether

NMR δ_{ppm} ($CDCl_3$) 1.28 (9H, s, t-Bu)
4.30 (1H, dd, J = 6 Hz and 1.5 Hz, )
4.65 (1H, dd, J = 13 and 1.5 Hz, )
6.54 (1H, dd, J = 6 and 13 Hz, )
6.82 and 7.25 (4H, ach d, J = 9 Hz, Ar)

p-methoxyphenyl-vinyl-ether

NMR δ ppm ($CDCl_3$) 3.60 (3H, s, OCH_3)

4.10 (1H, dd, J = 7 and 2 Hz, H)

4.52 (1H, dd, J = 14 and 2 Hz, H)

6.46 (1H, dd, J = 7 and 14 Hz, H)

6.8 (4H, br s, Ar)

p-chlorophenyl-vinyl-ether

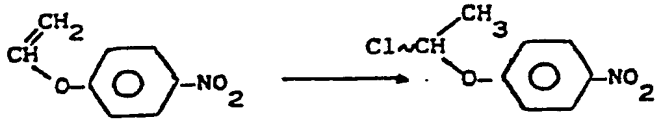
NMR δ ppm ($CDCl_3$) 4.53 (1H, dd, J = 4.9 and 1.8 Hz, H)

4.87 (1H, dd, J = 12 and 1.8 Hz, H)

6.60 (1H, dd, J = 12 and 4.5 Hz, H)

6.91 and 7.26 (4H, each d, J = 9 Hz, Ar)

Example 20
1-p-Nitrophenoxy-1-chloroethane



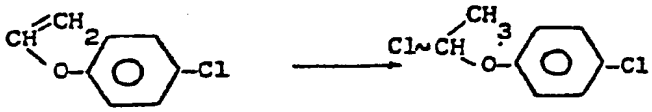
Dry hydrogen chloride was passed through a solution of p-nitrophenyl-vinyl-ether (0.42 g, 2.5 mmol) in tetrahydrofuran until T.L.C. (cyclohexane/ethyl acetate 3:1) showed complete conversion into a less mobile material (partial cleavage of the product to p-nitrophenol occurring on the silica gel plate).

Removal of the solvent afforded the product in quantitative yield.

NMR δppm ($CDCl_3$)

1.91 (3H, d, J=5 Hz, CH—CH_3)
6.45 (1H, q, J=5 Hz, CH—CH_3)
7.17 and 8.11 (4H, each d, J=9 Hz, Ar)

Example 21
1-p-Chlorophenoxy-1-chloroethane



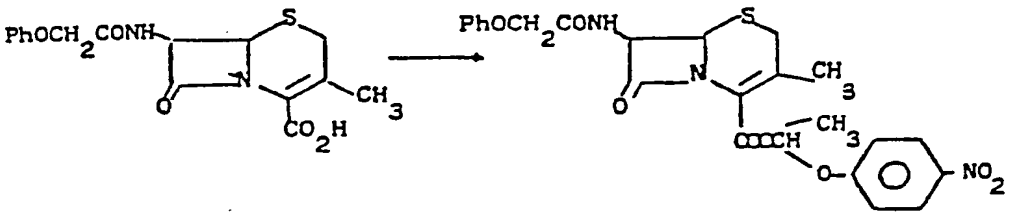
By following the experimental procedure described in Example 20 the title compound was obtained.

NMR δppm ($CDCl_3$)

1.90 (3H, d, J=5 Hz, CH_3—CH)
6.1 (1H, q, J=5 Hz, CH—CH_3)
6.95 and 7.28 (4H, each d, J=9 Hz, Ar)

Other (substituted)-phenoxy-1-chloroethanes, among which the p-acetylamino and p-*tert*-butyl ones, were obtained and immediately used.

Example 22
1-p-Nitrophenoxyethyl-7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate



A solution of 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylic acid (0.871 g, 2.5 mmol) and triethylamine (0.35 ml, 2.5 mmol) in acetonitrile (8 ml) was added to an ice-cold solution of 1-p-

nitrobenzyloxy-1-chloroethane (2.5 mmol) in a mixture of dichloromethane (3 ml) and acetonitrile (6 ml). After stirring for 15 hours, the mixture was partitioned between ethyl acetate and 8% aqueous $NaHCO_3$. The dried organic phase was evaporated and the residue crystallized from acetone/ethyl ether/petroleum ether, to obtain 0.74 g of the title ether as a white powder, m.p. 92—106°C (diastereoisomeric mixture).

IR ν_{max} (KBr) 3420, 3280, 1775, 1720, 1685, 1515, 1345, 1255, 1220, 1110, 1060, 750 and 690 cm^{-1}

NMR δppm ($CDCl_3$)

1.73 (3H, d, CH—CH_3)
2.11 (3H, s, :C—CH_3)
3.35 (2H, ABq, J=18.5 Hz, separation of inner lines 14 Hz, S—CH_2)
4.50 and 4.53 (2H, each s, O—CH_2—CO)
4.97 (1H, d, CH—*CH*—S)
5.81 (1H, m, NH—*CH*—CH)
6.6—7.4 (9H, m, Ar, *CH*—CH_3 and CONH)
8.15 (2H, d, Ar)

A similar procedure, starting from 7-phenoxyacetamido-3-ethyl-3-cephem-4-carboxylic acid and the appropriate halide, afforded the following esters:

1-p-Chlorophenoxyethyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate, m.p. 129—143°C;

IR ν_{max} (KBr) 3410, 3260, 1765, 1710, 1670, 1630, 1600, 1590, 1540, 1490, 1240, 1215 cm^{-1}

NMR δppm ($CDCL_3$)

1.67 (3H, d, CH—CH_3)
2.08 (3H, S, :C—CH_3)
3.36 (2H, ABq, J=18 Hz, separation of inner lines 14 Hz)
4.55 (2H, s, OCH_2CO)
4.77 (1H, d, J=4.5 Hz, CH—*CH*—S)
5.84 (1H, dd, J=4.5 and 8.0 Hz, NH—*CH*—CH)
6.66 (1H, q, *CH*—CH_3)
6.80—7.40 (10H, m, CONH and Ar)

1-p-Acetamidophenoxyethyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate, m.p. 156—175°C;

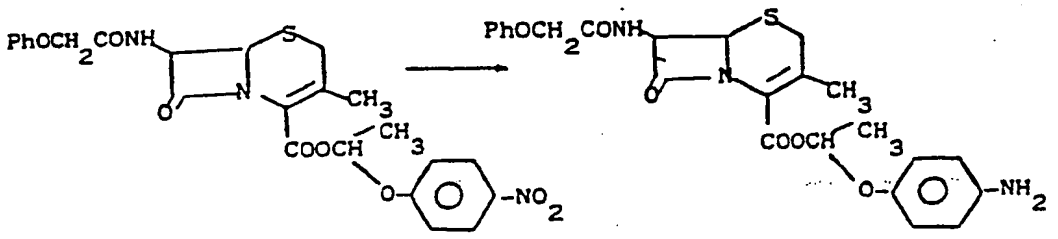
IR ν_{max} (KBr) 3410, 3260, 1770, 1710, 1670, 1600, 1535, 1510, 1490, 1240, 1210 cm^{-1}

NMR δppm ($CDCl_3$)

1.72 (3H, d, CH—CH_3)
2.12 (3H, s, :C—CH_3)
2.15 (3H, s, $COCH_3$)
3.55 (2H, ABq, J=14.5 Hz, separation of inner lines 18.0 Hz)
4.58 (2H, s, O—CH_2CO)
4.98 (1H, d, J=4.5 Hz, CH—*CH*—S)
5.87 (1H, dd J=8.0 and 4.5 Hz, NH—*CH*—CH)
6.56 (1H, q, *CH*—CH_3)
6.87—7.35 (11H, m, CONH and Ar)

Example 23

1-p-Aminophenoxyethyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate



A solution of 1-p-nitrophenoxyethyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (51 mg, 0.1 mmol) in dichloromethane (3 ml) was stirred for 15 minutes at room temperature in the presence of zinc dust (100 mg) and acetic acid (5 drops). The metal was filtered off and the solvent removed *in vacuo* to afford the title product in quantitative yield.

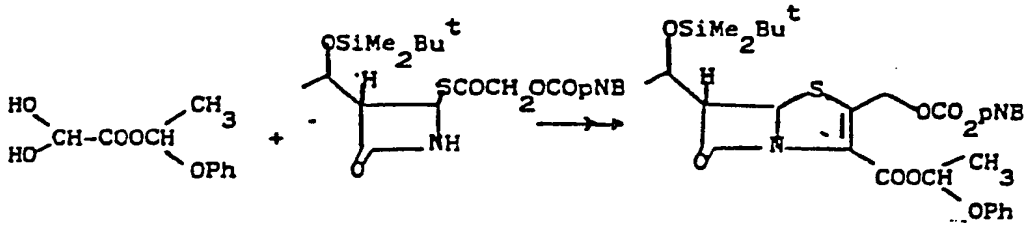
IR νmax ($CHCl_3$) 3420, 1785, 1720, 1690, 1625, 1600, 1510 and 1490 cm^{-1}

NMR δppm ($CDCl_3$)

1.64 (3H, d, CH—CH_3)
2.03 (3H, s, :C—CH_3)

3.22 (2H, ABq, J=17 Hz, separation of inner lines 6 Hz, S—CH_2)
4.03 (2H, br s, NH_2)
4.51 (2H, s, O—CH_2—CO)
4.95 (1H, d, J=4.5 Hz, CH—*CH_2*—S)
5.82 (1H, dd, J=4.5 and 8 Hz, NH—*CH*—CH)
6.55 (1H, q, *CH*—CH_3)
6.60—7.40 (10H, m, Ar and CONH)

Example 24
1-Phenoxyethyl (5*R*,6*S*)-6-[1(*R*)-tert-butyldimethylsilyloxyethyl] 2-p-nitrobenzyloxycarbonyloxymethyl-penem-3-carboxylate



Step a)
Glycolic acid (10 g), triethylamine (36.8 ml) and p-nitrobenzylchlorocarbonate (19.8 g) in dichloromethane (100 ml) were allowed to react for 1 hour at room temperature. Work-up, filtration through a short column of silica gel (CH_2Cl_2 as eluant) and crystallization from di-isopropylether gave 10.2 g of p-nitrobenzyloxycarbonyloxy acetic acid, m.p. 95—98°C.

Step b)
The product from step a), 5.4 g, was dissolved in dichloromethane (140 ml) in the presence of triethylamine (3 ml) and treated at −15°C with ethyl chlorocarbonate (2.1 ml).
After 20 minutes at room temperature, the mixture was cooled again, another portion of NEt_3 (3 ml) was added, and hydrogen sulphide was bubbled into the solution for 30 minutes at −15°C.
Work-up, extraction with aqueous $NaHCO_3$ and back-extraction with ethyl acetate after acidification, afforded impure p-nitrobenzyloxycarbonyloxythioacetic acid, which was used as such without further purification.

Step c)
The crude material from step b) was mixed with 3(*S*)-[1-(*R*)-tert-butyldimethylsilyloxyethyl]-4(*R,S*)-acetoxy-azetidin-2-one (2.81 g) in water/acetone and the pH of the solution was brought to 7.5—8.) by the addition of 1N NaOH. Work-up and chromatography after 1 hour afforded first some unreacted azetidinone and then 2.6 g of (3*S*)-[1(*R*)-tert-butyldimethylsilyloxyethyl]-4(*R*)-p-nitrobenzyloxycarbonyloxyacetylthioazetidin-2-one as a syrup.

Step d)
The material from step c), 700 mg, was refluxed with 1-phenoxyethyl glyoxylate hydrate (600 mg) in benzene, with slow azeotropic removal of the water released (Dean-Stark). After 4 hours the solvent was thoroughly evaporated to give 3(*S*)-[1(*R*)-tert-butyldimethylsilyloxyethyl]-4(*R*)-p-nitrobenzyloxycarbonyloxyacetylthio-1-[1-hydroxy-1-(1-phenoxyethyl)-oxycarbonyl]-methyl-azetidin-2-one as a mixture of diastereoisomers.

Step e)
1.1 g of the product from step d) was treated with pyridine (0.124 ml) and thionyl chloride (0.102 ml) in dry tetrahydrofuran (15 ml) for 30 minutes at 0°C. Filtration of the salt (Hiflo bed) and removal of any volatile material afforded crude 3(*S*)-[1(*R*)-tert-butyldimethylsilyloxyethyl]-4(*R*)-p-nitrobenzyloxycarbonyloxyacetylthio-1-[1-chloro-1-(1-phenoxyethyl)-oxycarbonyl]-methyl-azetidin-2-one.

Step f)
The material from step e) was treated with a solution of triphenylphosphine (1 g) and pyridine (0.12 ml) in dry THF.
Silica gel (4.6 g) was added and the solvent removed. After 2 hours standing, the powder was poured on top of a silica gel column. Elution with ethyl acetate/cyclohexane afforded 3(*S*)-[1(*R*)-tert-butyldimethylsilyloxyethyl]-4-(*R*)-p-nitrobenzyloxycarbonyloxyacetylthio-1-[1-triphenyl-phosphoranylidene-1-(1-phenoxyethyl)-oxycarbonyl]-methyl-azetidin-2-one as a white foam.

Step g)

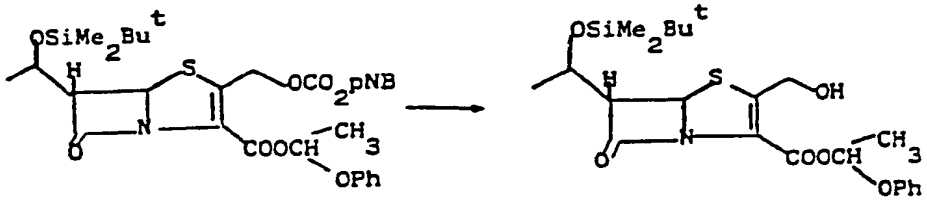
320 mg of the material from step f) was heated for 4 hours in dry toluene at 95—96°C. Removal of the solvent and chromatography afforded the title product (120 mg).

NMR δppm ($CDCl_3$)

0.06 (6H, s, $SiMe_2$)
0.87 (9H, s, Bu^t)
1.22 (3H, d, CH_3—CHOSi)
1.63 and 1.65 (3H, each d, CH_3—CHOCO)
3.69 and 3.71 (1H, each dd, J=2 and 4.5 Hz, CH—*CH*—CH)
4.22 (1H, m, CH_3—*CH*OSi—CH)
5.09 and 5.11 (1H, each d, :C—*CH*H—OCO)
5.26 (2H, s, O—CH_2—Ar)
5.51 and 5.51 (1H, each d, :C—CH*H*—OCO)
5.59 (1H, d, J=2 Hz, CH—*CH*—S)
6.55 and 6.62 (1H, each q, CH_3—*CH*OCO)
6.84—7.40 (5H, m, OC_6H_5)
7.50 and 8.20 (4H, each d, J=9 Hz, $C_6H_4NO_2$)

Example 25

1-Phenoxyethyl (5*R*,6*S*)-6-[1(*R*)-tert-butyldimethylsilyloxyethyl]-2-hydroxymethyl-penem-3-carboxylate



A solution of 1-phenoxyethyl (5*R*,6*S*)-6-[1(*R*)-tert-butyldimethylsilyloxyethyl]-2-p-nitrobenzyloxycarbonyloxymethyl-penem-3-carboxylate (120 ml) in ethyl acetate (6 ml) was stirred with 5% Pd/C under hydrogen for 1 hour. The catalyst was filtered off and the solvent removed. Chromatography of the residue (SiO_2, ethyl acetate/cyclohexane) afforded the title product.

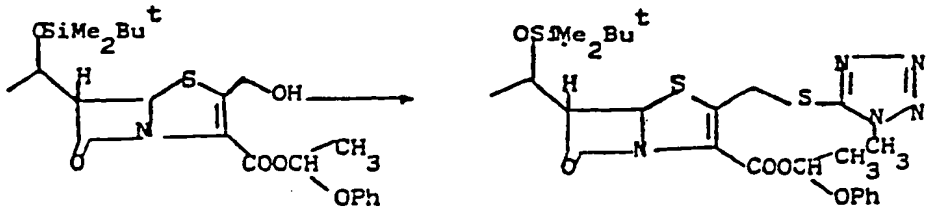
UV λ_{max} ($CHCl_3$) 328 nm (ε=6236)

NMR δppm ($CDCl_3$)

0.06 (6H, s, $SiMe_2$)
0.87 (OH, s, Bu^t)
1.20 (3H, d, CH_3—CHOSi)
1.62 and 1.64 (3H, each d, CH_3—CHOCO)
3.13 (1H, br s, OH)
3.64 and 3.66 (1H, each dd, CH—*CH*—CH)
4.19 (11H, m, CH_3—*CH*OSi—CH)
4.54 and 4.55 (2H, each s, CH_2OH)
6.52 and 6.55 (1H, each q, CH_3—*CH*—OCO)
6.85—7.4 (5H, m, Ar)

Example 26

1-Phenoxyethyl (5*R*,6*S*)-6-[1(*R*)-tert-butyldimethylsilyloxyethyl]-2-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl-penem-3-carboxylate

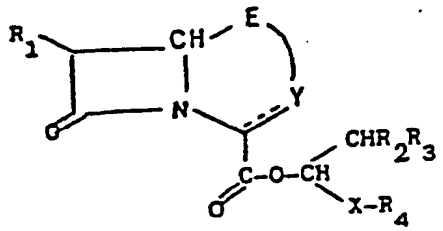


A solution of triphenylphosphine (60 mg) and di thylazodicarboxylate (36 ml) in dry tetrahydrofuran (2 ml) was stirred at 0°C for 30 minutes and then treated with a solution of 1-ph noxyethyl (5*R*,6*S*)-6-[1(*R*)-tert-butyldimethylsilyloxyethyl]-2-hydroxymethyl-penem-3-carboxylate (30 mg) and sodium 1-methyl-1,2,3,4-tetrazol-5-thiolate (22 mg) in dry tetrahydrofuran (1 ml). The

reaction mixture was fractioned by silica gel chromatography to afford 15 mg of the title product, identical by UV, IR and T.L.C. with the material obtained according to Example 14.

Claims

1. A compound of general formula (I)



(I)

wherein

R_1 is hydrogen, halogen or an organic group;

R_2 and R_3, being the same or different, are hydrogen or an organic group;

R_4 is an aromatic or heteroaromatic, monocyclic or bicyclic ring, unsubstituted or substituted by one or more substituents chosen from: C_1—C_6 alkyl, C_1—C_6 alkoxy, formyl, phenyl, phenoxy, C_2—C_6 alkanoyl, benzoyl, C_1—C_6 alkoxycarbonyl, amino unsubstituted or substituted by one or two C_1—C_6 alkyl, formylamino, C_2—C_6 acylamino, benzoyl-amino, halogen and nitro;

the symbol —E— represents —O—; —S— or —CH_2—;

X is oxygen or sulphur; and

the symbol  represents a group completing, with the group —E— and the fused azetidinone ring, the skeleton of a β-lactam antibiotic and the salts thereof.

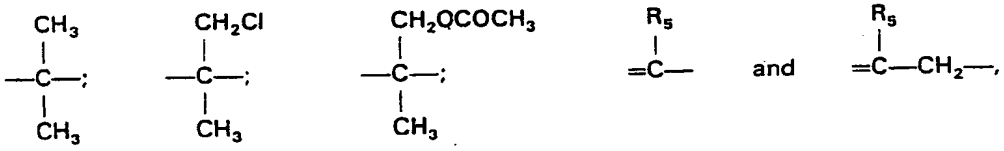
2. A compound of formula (I) according to claim 1 wherein:

R_1 is hydrogen, chlorine, bromine, amino, phenylacetamido, phenoxyacetamido, 2-amino-2-phenyl-acetamido, 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido, C_1—C_4 alkyl or 1-hydroxyethyl;

R_2 and R_3, being the same or different are hydrogen or C_1—C_6 alkyl;

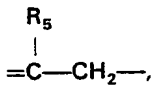
R_4 is phenyl, unsubstituted or substituted by 1, 2 or 3 substituents chosen from chlorine, nitro, methoxy, C_1—C_4 alkyl, amino, formamido, C_2—C_3 alkanoylamino;

X is oxygen; the symbol —E— represents —S— or —O—, wherein, when the symbol —E— represents —S—, the symbol represents a group chosen from:



and

wherein R_5 is an organic group, and wherein, when the symbol —E— represents —O—, then the symbol represents



wherein R_5 is as defined above; and the salts thereof.

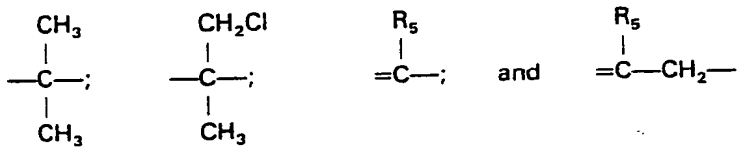
3. A compound of formula (I), according to claim 1, wherein:

R_1 is hydrogen, chlorine, bromine, amino, phenylacetamido, phenoxyacetamido, 2-amino-2-phenyl-acetamido, 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido, C_1—C_4 alkyl or 1-hydroxyethyl;

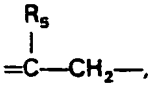
R_2 and R_3 are hydrogen;

R_4 is phenyl, p-nitrophenyl, p-aminophenyl, p-chlorophenyl, p-tolyl, p-tert-butylphenyl, p-acetamidophenyl;

X is oxygen; the symbol E represents —S— or —O—, wherein, when the symbol —E— represents —S—, the symbol represents a group chosen from:



and wherein, when the symbol —E— represents —O—, the symbol represents



wherein in both the cases R_5 is C_1—C_4 alkyl unsubstituted or substituted by a substituent chosen from:

a″) chlorine or bromine;

b″) a C_2—C_9 alkanoyloxy group;

c″) a carbamoyloxy group unsubstituted or substituted by one or two substituents chosen from C_1—C_4 alkyl and phenyl, and

d″) a —S—Het group, wherein Het denotes a heteromonocyclic or heterobicyclic ring chosen from the group consisting of thiazole, thiadiazole, tetrazole, triazine and tetrazolo-pyridazine, wherein said ring is in turn unsubstituted or substituted by 1, 2 or 3 substituents chosen from cyano, C_1—C_{12} alkyl, amino, bromine, chlorine, hydroxy, C_1—C_{12} alkoxy, formyloxy, C_2—C_{12} acyloxy, carboxy, C_1—C_{12} alkoxycarbonyl, and carbamoyl unsubstituted or substituted by one or two C_1—C_4 alkyl groups; and the salts thereof.

4. A compound of formula (I), according to claim 1, wherein:

R_1 is ethyl or 1-hydroxyethyl;

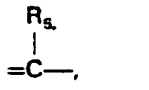
R_2 and R_3 are hydrogen;

R_4 is phenyl, p-nitrophenyl, p-aminophenyl, p-chlorophenyl;

X is oxygen;

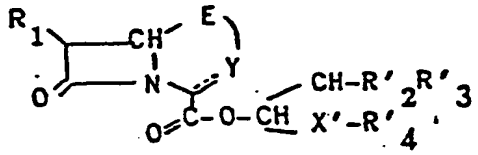
the symbol —E— is sulphur;

the symbol is a group



wherein R_5 is acetoxymethyl, carbamoyloxymethyl, (1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl, (1-carboxymethyl-1,2,3,4-tetrazol-5-yl)-thiomethyl, [1-(2-carboxy)ethyl-1,2,3,4-tetrazol-5-yl]thiomethyl, 2-(2-methyl-5-oxo-6-hydroxy-2,5-dihydro-1,2,4-triazin-3-yl)-thiomethyl, [1-(2-dimethylamino)-ethyl-1,2,3,4-tetrazol-5-yl]-thiomethyl, and the salts thereof.

5. A compound according to claim having the formula (Ia)

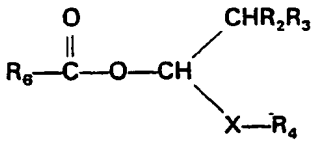


(Ia)

wherein R_1, —E— and the symbol  are as defined in claim 1, R'_2 and R'_3 are both hydrogen; X′ is oxygen; and R'_4 is phenyl, 4-methylphenyl, 4-chlorophenyl, 4-acetamidophenyl and 4-methoxyphenyl, and the pharmaceutically or veterinarily acceptable salts thereof.

6. A process for the preparation of a compound of formula (I) as claimed in claim 1, said process comprising:

A) joining a synthon of formula (II)



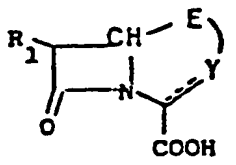
(II)

wherein

R_6 is a radical deriving from an α-aminoacid, an α-hydroxyacid, an α-keotacid, or an α-alkenoic acid, wherein the amino, hydroxy and keto groups are either free or protected with a protective group in current use in the field of peptides, and

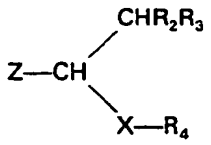
R_2, R_3, R_4 and X are as defined in claim 1, with another synthon, and then processing the obtained intermediate product along known *per se* procedures; or

B) reacting an acid of formula (III)



(III)

wh rein the symbols —E—, ⎓ Y and R_1 are as defined in claim 1, or a salt thereof, with a halide of formula (IV)



(IV)

wherein

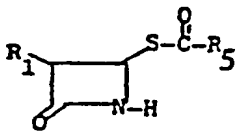
Z is chlorine, bromine or fluorine and R_2, R_3, R_4 and X are as defined in claim 1; and, if desired, converting a compound of formula (I) into another compound of formula (I); and/or, if desired converting a compound of formula (I) into a salt thereof; and/or if desired obtaining a free compound of formula (I) from a salt thereof; and/or, if desired, separating a mixture of isomers of formula (I) into the single isomers.

7. A process according to claim 6 for the preparation of a compound of formula (I) wherein —E— is sulphur and the symbol ⎓ Y is

wherein R_5 is as defined in claim 2, 3 or 4, wherein the process A) of claim 6 is carried out by:

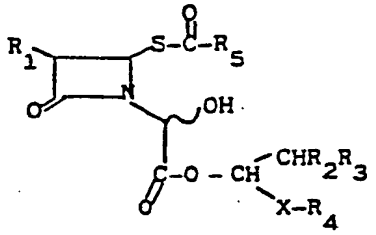
1') oxidizing a compound of formula (II), wherein R_6 represents the radical deriving from the L(+)tartaric acid, to give a compound of formula (II), wherein R_6 is formyl;

2') condensing said compound, or a hydrate, an acetal or hemiacetal thereof, with an azetidinone of formula (VI)



(VI)

wherein R_1 is as defined in claim 1 and R_5 is as defined in claim 2, 3 or 4, to obtain a compound of formula (VII)

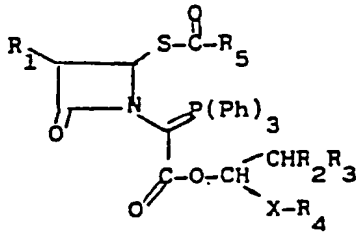


(VII)

wherein

R_1, R_2, R_3, R_4 and X are as defined in claim 1 and R_5 is as defined in claim 2, 3 or 4;

3') converting a compound of formula (VII) into a compound of formula (VIII)



(VIII)

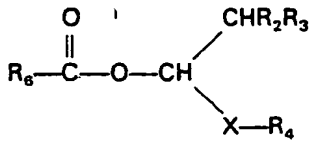
wherein

R_1, R_2, R_3, R_4 and X are as defined in claim 1, R_5 is as defined in claim 2, 3 or 4 and Ph represents phenyl; and

4') cyclizing a compound of formula (VIII) to obtain a compound of formula (I), wherein the symbol —E— represents —S— and the symbol ⎓ Y represents

wherein R_5 is as defined in claim 2, 3 or 4; and, if desired, converting an obtained compound of formula (I) into another compound of formula (I); and/or, if desired, converting a compound of formula (I) into a salt thereof; and/or, if desired, obtaining a free compound of formula (I) from a salt thereof; and/or, if desired, separating a mixture of isomers of formula (I) into the single isomers.

8. A compound of formula (II)



(II)

wherein

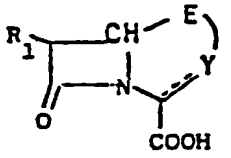
R_2, R_3, R_4 and X are as defined in claim 1, and R_6 is a radical deriving from an α-amino acid, an α-hydroxy acid, an α-keto acid, or an α-alkenoic acid, wherein the amino, hydroxy and keto groups are free or protected.

9. A compound of formula (II), according to claim 8, wherein R_2, R_3, R_4 and X are as defined in claim 3 and R_6 is a radical deriving from tartaric acid, fumaric or glyoxylic acid.

10. A compound having the formula (VII) reported above in claim 7, wherein R_1, R_2, R_3, R_4 and X are as defined in claim 7.

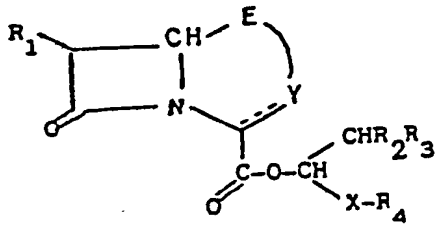
11. A compound having the formula (VIII) reported above in claim 7 wherein R_1, R_2, R_3, R_4, R_5 and X are as defined in claim 7.

12. A process for the preparation of a compound of formula (III), or a salt thereof



(III)

wherein the symbols —E—, ⌒Y⌒ and R_1 are as defined in claim 1, said process comprising the cleavage of an ester of formula (I)



(I)

wherein the symbols —E—, ⌒Y⌒, R_1, R_2, R_3, R_4 and X are as defined in claim 1.

13. A process for the preparation of a compound of formula (III), according to claim 12, wherein the cleavage of the ester of formula (I) is carried out by hydrolysis.

14. A process according to claim 13 wherein the hydrolysis is an acid hydrolysis.

15. A process according to claim 14 wherein the acid hydrolysis is carried out by a Lewis or a Brönsted acid.

16. A process according to claim 15 wherein the Lewis acid is selected from the group consisting of $AlCl_3$, BF_3, $ZnBr_2$, $ZuCl_2$, $SnCl_4$ and $FeCl_3$.

17. A process according to claim 15 wherein the Brönsted acid is selected from the group consisting of trifluoroacetic acid, formic acid, oxalic acid, acetic acid and citric acid.

18. A pharmaceutical or veterinary composition containing a suitable carrier and/or diluent and, as the active principle, a compound having the formula (Ia) reported above in claim 5 or a pharmaceutically or veterinarily acceptable salt thereof.

19. A compound according to claim 1, 8, 10 or 11 specifically identified herein.

20. A process according to claim 6 substantially as described in any one of Examples 1 to 6, 8, 10 to 14, 16, 17 and 19 to 26.

21. A process according to claim 12 substantially as described in any one of Examples 7, 9, 15 and 18.

22. A compound of formula (Ia) or pharmaceutically or veterinarily acceptable salt thereof according to claim 5 for use as an anti-bacterial agent.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1984. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.